Université de Montréal

Timely Treatment Initiation of Free Drug-Resistant Tuberculosis Care in Nigeria? A Mixed Methods Study of Patient Experience, Socio-demographic Characteristics and Health System Factors

Par

Charity Oga-Omenka

Département de médecine sociale et préventive, École de santé publique, Université de Montréal

Thèse présentée en vue de l'obtention du grade de Philosophiae Doctor (PhD)
en Santé Publique, option Santé Mondiale, de l'Université de Montréal en santé publique,

Juillet, 2020

Université de Montréal

Faculté des études supérieures et postdoctorales

Cette thèse intitulée:

Timely Treatment Initiation of Free Drug-Resistant Tuberculosis Care in Nigeria? A Mixed Methods Study of Patient Experience, Socio-demographic Characteristics and Health System Factors

Présenté par
Charity Oga-Omenka

A été évaluée par un jury composé des personnes suivantes

Pierre Fournier
Président-rapporteur

Christina Zarowsky
Directrice de recherche

Richard Menzies
Codirecteur

Thomas Druetz
Membre du jury

Brittney van de Water
Examinatrice externe

RÉSUMÉ

Introduction: Au Nigeria, la couverture de la détection et du traitement de la tuberculose pharmaco-résistante (TPR) est toujours faible malgré la mise en place de services gratuits depuis 2011. Le pays se classe au sixième rang mondial avec une proportion de cas de patients résistants aux médicaments de 4,3% et de 15% dans les cas d'une réinitialisation au traitement. Le pays a aussi un fardeau élevé pour la tuberculose, la TPR, et le VIH, avec une prévalence de 219 et 11 pour 100 000 habitants pour la tuberculose et la TPR et de 1,28 pour 1 000 habitants pour le VIH. Sans traitement, la mortalité due à la tuberculose est d'environ 70% en dix ans, augmentant avec la coïnfection par le VIH, et la résistance aux médicaments; et descendant en dessous de 5% avec traitement. Les taux de survie de la tuberculose pharmaco-résistante sont plus faibles et le traitement est plus long, plus coûteux et plus toxique. Cela peut poser des défis différents à la fois pour les patients et les systèmes de santé comparativement à la tuberculose de la forme commune. Cependant, la réponse au traitement et la survie sont influencées par la détection précoce et à l'initiation rapide au traitement, idéalement dans les quatre semaines suivant le diagnostic, en particulier avec la coïnfection par le VIH. Les caractéristiques sociodémographiques interagissent souvent de manière complexe avec des facteurs systémiques, pour accroître la vulnérabilité et les désavantages - ces interactions sont particulièrement bien examinées à travers un cadre conceptuel d'équité à l'accès à la santé, et pourrait offrir des analyses et des recommandations pertinentes pour les politiques. Cette thèse explore les barrières et les facilitateurs à l'accès au diagnostic et au traitement au niveau des patients et du système de santé au Nigéria.

Méthodes: Cette thèse est une étude transformative de méthodes mixtes. Nous avons d'abord réalisé une revue systématique mixte pour identifier les obstacles et les facilitateurs influençant l'accès au diagnostic et au traitement de la TPR en Afrique subsaharienne. Nous avons par la suite mené une méta-synthèse qualitative pour examiner en profondeur les obstacles aux soins de la tuberculose auxquels se heurtent les patients, la communauté, et le système de santé. Nous avons utilisé les résultats des deux revues systématiques pour affiner notre cadre conceptuel afin

d'orienter la conception et l'analyse de l'étude empirique qui a suivi. Le cadre conceptuel adapté est basé sur le cadre de Levesque. Ce cadre centré sur les patients conceptualise l'accès aux soins selon des dimensions du système de santé et des patients.

Cette étude comprenait également une analyse rétrospective d'une cohorte de patients diagnostiqués en 2015 (n = 996) à l'aide de données secondaires nationales et une analyse en cascade des soins de la tuberculose pharmaco-résistante entre 2013 et 2017. Nous avons mené des analyses statistiques descriptives et analytiques. Nous avons effectué une régression logistique et d'autres tests d'association pour mesurer la relation entre les variables catégorielles.

L'étude qualitative était une étude de cas qui consistait à examiner la dynamique de soins du point de vue des patients (n = 86 participants, n = 7 groupes de discussions, 5 entretiens approfondis avec des patients diagnostiqués et non traités), leurs familles (n = 19 participants, n = 1 groupe de discussion, 7entretiens approfondis), membres de la communauté (n = 23 , n=2 groupes de discussion), agents de santé (n = 5 entretiens approfondis) et gestionnaires de programme (n = 29 entretiens approfondis) dans quatre États du Nigéria. Nous avons analysé nos données qualitatives à l'aide d'une analyse thématique.

Résultats: Notre revue systématique mixte et notre méta-synthèse qualitative ont indiqué des obstacles et des facilitateurs à l'accès aux soins de la tuberculose pharmaco-résistante au niveau du système de santé et des patients. Les problèmes de fonctionnement des laboratoires et des cliniques, l'absence de connaissances et les attitudes des prestataires de soins, et la gestion de l'information étaient des obstacles à l'accès aux soins de la TPR. Les facteurs facilitateurs comprenaient des outils de diagnostic plus récents, la décentralisation des services et le coût gratuit des soins. Au niveau des patients, la perte de suivi avant ou pendant les soins en raison de la perception négative des soins dans les services publics, le genre, la famille, l'engagement professionnel ou scolaire, et le recours aux soins dans le secteur privé constituaient des obstacles. Les facilitateurs étaient la séropositivité pour VIH, la multitude de symptômes, et le soutien financier des patients.

Nos résultats quantitatifs ont révélé une certaine amélioration mais des progrès insuffisants dans le diagnostic et la couverture du traitement au Nigeria entre 2013 et 2017. Notre analyse en cascade a montré des abandons significatifs entre chaque étape des soins, en commençant par les tests et en terminant par l'achèvement du traitement. En moyenne, 80% des cas estimés n'ont pas eu accès au test; 75% de ceux qui ont été testé n'ont pas été diagnostiqués; 36% des personnes diagnostiquées n'ont pas commencé le traitement et 23% d'entre elles n'ont pas terminé le traitement pour la période entre 2013-2017.

En 2015, les patients et les enfants atteints de la TB qui résident au nord du Nigéria avaient une probabilité de 0,3 [IC à 95% 0,1-0,7] et 0,4[0,3-0,5] de terminer le traitement une fois la maladie diagnostiquée comparativement aux patients et aux enfants qui résident au sud du pays. Les hommes avaient une probabilité de 1,34 [IC à 95% 1,0-1,7] plus élevée de terminer le traitement après le diagnostic comparativement aux femmes. La localisation géographique et les niveaux de soins étaient associés à un traitement et / ou à un traitement rapide.

Notre étude qualitative a identifié des obstacles aux soins aux niveaux individuel, familial, communautaire, et du système de santé. Certains groupes sociodémographiques de patients avaient un accès inéquitable aux soins de la TPR. Alors que les patients étaient pour la plupart traités de manière égale au niveau de l'établissement, certains patients avaient plus de difficulté à accéder aux soins en fonction de leur sexe, de leur âge, de leur profession, de leur niveau d'éducation, et de leur religion. La dynamique familiale et conjugale influencent l'accès aux soins des patients, en particulier des enfants et des femmes. Elle agissait parfois comme un obstacle aux soins.

D'autres facteurs qui ont probablement entravé l'accès incluaient l'absence de considérations sur les droits d'accès et la protection des patients dans les directives de traitement et les protocoles de soins. Les patients ignoraient pour la plupart les causes de la tuberculose pharmaco-résistante et la disponibilité des soins gratuits. Le nombre d'agents de santé et les problèmes de formation, la faible performance des laboratoires et des cliniques sont des obstacles aux soins de la tuberculose au niveau du système de santé. Les principaux facilitateurs à l'accès aux soins comprenaient le soutien familial, le soutien financier aux patients et le traitement gratuit.

Conclusions: Malgré la gratuité des tests et des traitements de la TB pharmaco-résistante au Nigéria depuis 2011, les couvertures de diagnostic et de traitement restent constamment faibles.

Les obstacles à l'accès au diagnostic et au traitement de la TB et de la TB pharmaco-résistante sont similaires. Toutefois, la TB pharmaco-résistante présente des défis particuliers en raison de la complexité des procédures de prétraitement et des toxicités résultant des médicaments eux-mêmes. Notre étude avait pour objectif de mieux comprendre les facteurs qui influencent l'accès à l'initiation au traitement de la TB pharmaco-résistante. Nos résultats montrent que les obstacles les plus importants sont l'accès aux tests et au diagnostic, malgré les progrès technologiques de diagnostic et des protocoles cliniques. Notre étude a identifié plusieurs obstacles liés aux patients et au système de santé. La plupart des patients atteints de TB pharmaco-résistante n'ont pas accès aux tests et ne sont pas diagnostiqués, souvent en raison d'un manque d'information.

Les politiques et les programmes de lutte contre la tuberculose pharmaco-résistante ne sont pas toujours équitables, en particulier pour les populations vivant dans les zones rurales, les enfants, et les femmes. Les résultats de notre étude ont généré des données probantes pertinentes pour les décideurs et les partenaires internationaux pour remédier aux disparités systémiques et fournir des services plus équitables. L'élimination des obstacles à l'accès aux soins en temps opportun devrait être une priorité urgente pour améliorer le programme de lutte contre la tuberculose au Nigéria. Dans la faible détection des cas et la couverture thérapeutique, les interventions devraient viser l'équité en facilitant l'accès aux soins des populations vulnérables.

Mots-clés: Tuberculose pharmaco-résistante, diagnostic, traitement, accès aux soins, barrières et facilitateurs, cascade de soins, équité, soins de santé primaires, systèmes de santé, santé mondiale, revue systématique, méta-synthèse qualitative, méthodes mixtes, Nigeria, Afrique sub-Saharienne.

ABSTRACT

Background: Detection and treatment coverage for drug-resistant tuberculosis (DR-TB) in Nigeria are persistently low despite the implementation of free diagnostic and treatment services since 2011. Nigeria has a high burden for tuberculosis, ranking 6th globally with 4.3% drug resistance in new, and 15% in retreatment cases. The World Health Organization classifies the country as a high burden for TB, DR-TB, and HIV, with a prevalence of 219 and 11 per 100,000 population for TB and DR-TB, and 1.28 per 1,000 population HIV. Without treatment, mortality from tuberculosis is approximately 70% within ten years, increasing with HIV co-infection and drug resistance - and decreasing to below 5% with treatment. DR-TB survival rates are lower, and treatment is longer, costlier, and more toxic; this may pose different challenges to both patients and health systems than is the case for drug-sensitive (DS-) TB. However, treatment response and survival are positively impacted by early detection and treatment initiation, ideally within four weeks of diagnosis, especially with HIV co-infection. Socio-demographic characteristics often interact in complex ways with systemic factors, to increase vulnerability and disadvantage – these interactions are particularly well examined through an equity of health access framework and could offer policy-relevant analyses and recommendations. This study explores patient and health system barriers and facilitators to diagnosis and treatment for DR-TB in Nigeria.

Methods: This is a sequential transformative mixed-methods study. First, a mixed-methods systematic review identified barriers and facilitators affecting diagnosis and treatment for DR-TB in sub-Saharan Africa. A subsequent qualitative meta-synthesis was used to examine in more depth the patient, community, and health system barriers to TB care. The results of the systematic reviews were used to refine our conceptual framework and to guide the design and the analysis of the subsequent empirical study. The adapted conceptual framework is based on the Levesque framework for patient-centred healthcare access, which conceptualises access to care as having health system and patient dimensions.

This study also included a retrospective cohort analysis of patients diagnosed in 2015 (n= 996)

using National secondary data, and a DR-TB care cascade analysis of the period between 2013 and 2017. We used descriptive statistics, logistic regression and other tests of association to measure the relationship between variables categorical. The qualitative phase used a case study design to examine the dynamics of care from patients' perspectives (n= 86 participants, N= 7 focus group discussions (FGD), 5 in-depth interviews (IDIs) with diagnosed and untreated patients), their relatives (n= 19 participants, N= 1 FGD, 7 IDIs), community members (n=23 in 2 FGDs), healthcare workers (n= 5 IDIs), and program managers (n= 29 IDIs) in four States in Nigeria. We analysed our qualitative data using thematic analysis.

Results: Our mixed methods systematic review and qualitative meta-synthesis revealed barriers and facilitators to DR-TB care at the health system and patient levels. Health system laboratory and clinic operational issues, poor provider knowledge and attitudes and information management were some barriers. Facilitators included newer diagnostic tools, decentralisation of services and free cost of care. At the patient level, loss to follow-up before or during care due to negative public sector care perceptions, gender, family, work or school commitments and using private sector care were some barriers. Facilitators were HIV positivity, having more symptoms, and financial support.

Our quantitative findings revealed some improvement but inadequate progress in diagnosis and treatment coverage in Nigeria between 2013 and 2017. Our cascade analysis showed significant dropouts between each stage of care, starting with testing and ending with treatment completion. On average, between 2013-2017, 80% of estimated cases did not access testing; 75% of those who test were not diagnosed; 36% of those diagnosed were not initiated on treatment and 23% of these did not finish treatment. In 2015, children and patients in Northern Nigeria had odds of 0.3 [95% CI 0.1-0.7] and 0.4 [0.3-0.5] of completing treatment once diagnosed; compared with adults and patients in Southern Nigeria; while males were shown to have a 1.34 [95% CI 1.0-1.7] times greater chance of completing treatment after diagnosis compared to females.. Geographic locations and levels of care were associated with ever receiving treatment and or timely treatment. Our qualitative data and document review identified barriers to care at individual, family, community, and health systems levels. Some patient socio-demographic

groups had inequitable access. While patients were mostly treated equally at the facility level, some patients experienced more difficulty accessing care based on their gender, age, occupation, educational level and religion. Parental and spousal influences affected patients, particularly children, and women, and were sometimes barriers to care. Other factors that likely hampered access include the absence of considerations for patients' access rights and protection in the treatment guidelines and workers manuals. Patients were mostly unaware of the causes of DR-TB disease and the availability of free care. Health worker numbers and training, clinic, and operational laboratory issues limited patients' access at the health system level. The main facilitators to care included family support, patient financial support, and free treatment.

Conclusions: Despite the provision of free DR-TB testing and treatment in Nigeria since 2011, coverage for diagnosis and treatment remain persistently low. Our literature review identified many of the same access factors affecting both DS-TB and DR-TB. However, DR-TB had peculiar challenges due to complexities in pre- treatment procedures, and in toxicities as a result of the medications themselves. This study was designed to investigate the access factors impacting DR-TB treatment initiation identified in literature. However, our findings showed that the biggest barriers to DR-TB care were essentially in access to testing and diagnosis, making any advances in diagnostic technology and treatment regimens of little benefit to DR-TB patients in Nigeria. Several patient and health system factors were shown to impede access to DR-TB care, particularly for certain groups of patients. Most DR-TB patients are not accessing testing and do not get diagnosed, often due to a lack of information. Also, DR-TB policies, structures and processes are not always equitable, especially for rural dwellers, children and women. Findings from our mixed methods study provided the additional insights needed by policymakers and implementing partners to address systemic disparities and provide more equitable services based on the population's needs. Eliminating barriers that negatively impact timely access to care should be an urgent priority for the TB program in Nigeria. In Nigeria's low case-finding and treatment coverage, interventions should target equity and ease of access, specifically for the barriers identified at the patient and health system levels.

Keywords: Drug-resistant tuberculosis, access to care, diagnosis, treatment, barriers and facilitators, cascade of care, equity, primary health care, health systems, global health, systematic review, qualitative meta-synthesis, Nigeria, Mixed methods, sub-Saharan Africa.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CC	Case Control
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COREQ	Consolidated criteria for reporting qualitative research for qualitative studies
CSDH	Commission on Social Determinants of Health
DR-TB	Drug- resistant tuberculosis
DST	Culture/Phenotypic Drug Susceptibility Testing
EMBASE	Evidence-based Medicine
FGD	Focus Group Discussion
HBC	High Burden Country
HCW	Health care Worker
HIV	Human Immunodeficiency Virus
ID #	Identification Number
IDI	In-depth Interview
IJTLD	International Journal of Tuberculosis and Lung Disease
IQR	Interquartile Range
KII	Key Informant Interview
KSA	Knowledge, Skills and Attitudes
LPA	Line Probe Assay
LTAT	Laboratory Turnaround Time
MDR-TB	Multi-Drug Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MMAT	Mixed Methods Appraisal Tool

MTBDRPlus	Molecular assay for detection of Mycobacterium tuberculosis and drug resistance
MTB/RIF	Mycobacterium tuberculosis and drug resistance
NA	Not Applicable
NRL	National or Central Reference Laboratory
OR	Odds Ration
PICO	Population, Intervention and Comparator Outcomes
PLWH	People Living with HIV
RR	Risk Ratio
RR-TB	Rifampicin-Resistant Tuberculosis
SDG	Sustainable Development Goals
SL	Second Line
SSA	Sub-Saharan Africa
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TAT	Turnaround Time
TTI	Time to Treatment Initiation
TTT	Time to Treatment
TB	Tuberculosis
UN	United Nations
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis
Xpert	GeneXpert MTB/RIF

ACKNOWLEDGEMENTS

It has been a privilege to be mentored by Christina Zarowsky. Our journey started with her supervising my MPH at the University of the Western Cape, South Africa, and continued after my family moved to Montreal so I could start a PhD with her supervision. Under her tutelage, I developed a passion for qualitative research methods and investigating health issues from human viewpoints, which developed into a healthy appreciation for mixed methods health research. This PhD could not have been possible without her.

I also acknowledge Richard Menzies (McGill University), my co-supervisor, for guiding me in TB research designs and for his invaluable contribution to the quantitative phase of this thesis. His passion and dedication to improving the lives of TB patients has been inspiring.

I owe gratitude to the National TB and Leprosy Control Program (NTBLCP) of the Nigerian Federal Ministry of Health, as well as the International Research Center for Excellence (IRCE) of the Institute of Human Virology Nigeria (IHVN). I'm thankful to have been granted access to their databases and for all the support I received in the process of data collection. I am grateful to my former bosses and colleagues at IHVN, especially Patrick Dakum, Aderonke Agbaje, the South-West Regional and the Central Offices, for supporting me through every stage of this research, and for all the resources they made available to me.

I am also thankful for research and conference travel funding received from the Global Fund MDR-TB Grant through IHVN, Canadian Institutes of Health Research (CIHR), *Institut de recherche en santé publique* (IRSPUM) and *Centre de recherche du Centre hospitalier* (CRCHUM) of the University of Montreal, and the Leacross and Teasdale Corti Foundations.

The role of McGill International TB Centre has been huge especially during the data analysis and manuscripts preparation phase of my PhD. I extend my profound gratitude to Madhukar Pai, for hiring me to manage the Centre, which granted me access to very rich TB research resources, and for giving me the push and encouragement I needed to cross the finish line. The idea for the Cascade paper came directly from my interactions with colleagues at the Centre. I thank Amrita, Caroline, Danielle, Tripti, Paulami, Petra, Sophie and the rest of the awesome Pai TB team - for their constant collaborative work and validations.

I am grateful to my Global Health classmates, *les mousquetaires* – Muriel, Stella, Cielo, and Rolande. We 'battled' the PhD qualifying exams together. You asked hard questions and made numerous invaluable inputs to the thesis protocol. Not forgetting my other very dear course mates: Fereshteh, Amelie, Victor, Isidore, and Jean-Claude. I also thank very specially Loubna, Nafeesa, Lara and Adeline: for giving me practical examples on how to get through a PhD.

Thank you, Mom, Margaret Oga for your unconditional love and for modelling perseverance before me daily. Watching you do the seemingly impossible, watching you joggle many balls while doing your PhD has been my source of inspiration. I'm grateful to my late father, Job Oga; for instilling in me value for hard work and love for God and family. I thank my siblings: Edna, Steve, Evie, Ruth and Emmanuel and their families - for providing a place of escape and extreme fun through the years. I love you guys, every single one of you.

It was to be a double celebration for my extended family which was cut short by the sudden death of my sister in-law Achilla Mary Idikwu, a week before her PhD defense on June 15th. I dedicate this thesis to her memory and honor of her legendary hard work.

I thank my friends and their family in Canada and Nigeria- Owa, Benga, Martha, Uregwu, Temi, E-grace, the Gimbas, Okpayi, Elahs, Nguavese, Adeola, Christie, Crown and Omenka – to name a few, for supporting my family and I through this journey.

Besides me, one person bore the full brunt of this PhD - my husband Emmanuel. Sweetheart, you know I could never have done this without you. You have been the rock I have rested my whole weight on. Thank you for your push, your patience and your love. This is to us.

Finally, I dedicate this PhD to the true heroes of my journey, my daughters- Zoe, Zemani and Zara- and the future impossible endeavours they will undertake. Immigrating at very young ages, with a crazy Mom, you have learnt to navigate a new world and do so much, almost all by yourselves. I love you fiercely and I am so proud of the beautiful young ladies you are becoming.

CHAPTER 1: GENERAL INTRODUCTION

Foreword

Nigeria is a high burden country for tuberculosis (TB), drug-resistant (DR-) TB and HIV. Life-saving medications to treat TB are increasingly rendered less effective by drug-resistance. Despite the fact that the country provides free diagnostic and treatment services since 2011, case detection and treatment rates are among the lowest in the world, threatening global TB control.

This thesis, in the global health option of a doctorate in public health, used mixed methods to: explore health system and patient factors that influence diagnosis and treatment for DR-TB, describe dropouts and factors associated with attrition between each stage of the DR-TB care cascade; and discuss whether the policies, structures and procedures for DR-TB support the diagnosis and treatment in Nigeria for different patient socio-demographic groups.

The study focuses on DR-TB diagnosis and treatment coverage in Nigeria, as this has remained much lower than for drug susceptible TB (WHO, 2019a). Treatment protocols for DR-TB are also more complex than for drug-sensitive TB, and studies have confirmed that these DR-TB protocols are more difficult for health systems to implement and for patients to complete due to their higher toxicity and longer durations (Cazabon et al., 2017a, EUI, 2019, WHO, 2017c, WHO, 2019e).

The overall purpose of this this dissertation was to understand reasons for low case detection and treatment rates for DR-TB in Nigeria. It was designed to answer the following questions: 1) What are the health system and patient factors that influence diagnosis and treatment for DR-TB in Nigeria? 2) What are the percentage dropouts and factors associated with attrition between each stage of the DR-TB care cascade? 3) Do the policies, structures and procedures for DR-TB support the diagnosis and treatment in Nigeria for different patient socio-demographic groups?

This introduction will present an overview of the global TB burden and the particular challenge of DR-TB; the influence of socio-demographic characteristics on health; the concept of equity of healthcare access; the context of the study; study purpose, questions and objectives; the researcher background and the structure of the thesis.

Our mixed methods study starts with a critical review of literature in 2 parts: a mixed methods systematic review of literature from sub-Saharan African countries; and a qualitative meta-synthesis of studies from Nigeria (articles 1 and 2). This is followed by three empirical articles on the quantitative, qualitative and mixed methods components of our study (articles 3, 4 and 5).

1.1. Global tuberculosis burden

According to the 2019 Global Tuberculosis report, there were an estimated 10 million new cases worldwide in 2018, of which 57% were among men, while 32% and 11% were among women and children respectively (WHO, 2019a). An estimated 1.5 million deaths occurred, surpassing Human Immunodeficiency Virus (HIV) and making tuberculosis (TB) the leading cause of death from an infectious disease (WHO, 2019a). This is despite the fact that most people who develop TB disease can be cured if they are diagnosed early and placed on the correct treatment. Without treatment, studies of the natural history of TB disease report a fatality rate of approximately 73% within 10 years (Tiemersma et al., 2011). With treatment, this can be below 5% (WHO, 2019a). The likelihood of dying from TB disease increases with HIV co-infection and drug-resistance (Gandhi et al., 2010b).

Sixty percent of the new cases in 2018 were in six countries : India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (6%) and Nigeria (4%), making them crucial to the attainment of the End TB Strategy milestones and the Sustainable Development Goals (SDG) (WHO, 2019a).

The End TB Strategy and SDG targets for 2030 can only be met when the annual decline in the global TB incidence rate is accelerated to an average of 17% per year (WHO, 2019a). The rate incidence decline was only about 2% on average between 2014 to 2018, where a 4–5% annual decline was required (WHO, 2020b). This was attributed to an estimated 3 million gap in detection, with India (25%), Nigeria (12%) and Indonesia (10%) accounting for about half (WHO, 2019a).

In the same report, the World Health Organization (WHO) updated three lists of high burden countries (HBC) for the period 2016–2020: one for TB, one for drug resistant TB and one for TB/HIV. Each list included 30 countries that met a minimum threshold of incident cases (10,000 per year for TB, and 1,000 per year for TB/HIV and DR-TB). Each list accounts for 87–90% of the global burden, with almost all in the top 20 countries. While 48 countries appear in at least one list with overlaps between lists, 14 countries appear in all three. Nigeria is one of these high burden countries for TB, drug-resistant TB and HIV (WHO, 2019a).

The emergence of Sars-Cov2 infection in 2020 has introduced a significant new threat to health systems globally, particularly TB care in low and middle-income countries. Several models predicted the huge COVID-19 disruptions in TB care (Bhargava and Shewade, 2020, Cilloni et al., 2020, Glaziou, 2020, McQuaid et al., 2020) that are now being confirmed by new reports (TB Civil Society Organizations, 2020, GFATM, 2020, StopTB Partnership, 2020, WHO, 2020a).

1.2. The particular challenge of drug-resistant tuberculosis

Antimicrobial agents, critical to fighting planetary diseases of humans, animals and plants, are increasingly threatened by resistance, rendering many diseases untreatable and life-saving procedures riskier (WHO, 2019c). Antimicrobial resistance causes at least 700,000 deaths yearly and threatens the achievement of several global health goals, including the SDGs and Universal Health Coverage (WHO, 2019c).

Drug-resistant tuberculosis (DR-TB) actively infected an estimated 484,000 people, and took 214,000 lives in 2018 alone, accounting for one third of all deaths from antimicrobial resistance and threatening to reverse years of advances in global TB control (WHO, 2019a, WHO, 2019c, Pai and Memish, 2019). The World Health Organization (WHO) estimated that 3.4% of new cases and 18% of previously treated people had DR-TB in 2018. It continues to be a major global challenge especially in settings where healthcare systems are fragmented (Gandhi et al., 2010a, WHO, 2019a), because – as discussed below and throughout the thesis – DR-TB reflects and in fact is often “created” by health system failures at every step from prevention, to testing, to diagnosis, to treatment initiation, to successful completion of treatment (Albanna and Menzies, 2011, Sharma and Mohan, 2006).

DR-TB is defined as strains of TB that are resistant to rifampicin or to both isoniazid and rifampicin. Much DR-TB results from human-made errors including poor management of susceptible TB infections, and delayed, inadequate access or substandard TB medications, as well as poor adherence (Pai, 2019, WHO, 2014a). It continues to spread today through airborne transmission and is fuelled by delayed access to DR-TB care (WHO, 2014a, Kendall et al., 2019).

Compared to drug susceptible (DS-) TB, DR-TB is more challenging to prevent, diagnose and treat (WHO, 2014a). Survival rates are lower, with a 44% mortality rate on average, and treatment is often lengthy with multiple, potentially toxic drugs that are up to five times costlier, and results in poorer treatment outcomes (WHO, 2019a, EUI, 2019, WHO, 2017c, WHO, 2018c). Additionally, patients face catastrophic economic and social costs while seeking care and while on treatment. However, evidence shows that response and survival are positively impacted by treatment within 4 weeks of diagnosis, as mortality rate is highest within the first month of diagnosis, especially for those co-infected with HIV (Turett et al., 1995, Gandhi et al., 2010b). The WHO also recommends early detection and quality treatment as a way to curb the spread (WHO, 2014a).

As with DS-TB, case detection and initiation of treatment are important problems for DR-TB. In 2018, only about 39% of incident DR-TB cases were detected globally, out of which only 32% were placed on treatment. Nigeria is one of 10 countries contributing 75% of the global gap in detection and treatment of DR-TB (WHO, 2019a).

1.3. The influence of patient socio-demographic characteristics on health

Literature indicates that the burdens of infectious diseases like TB are disproportionately borne by patients with certain socio-demographic characteristics, especially in low and middle-income countries (Farmer, 1996, Bhutta et al., 2014b). For example, rural patients bear higher treatment costs and report more difficulty with transport to health centers for treatment. The incidence and impacts of TB are also gendered, not only in the biological differences between males and females but also in the many behaviours, expectations and roles attributed to women and men through social and cultural frames (Ridgeway, 2009). Although TB incidence is significantly higher in men than in women (WHO, 2019a, FMOH, 2012b), women are more negatively impacted from adverse gender roles and limited property rights that limit health decision-making, and access to healthcare and education (Farmer, 1996, Folbre, 2014, Oshi et al., 2016a); increased care-giving and financial burden when members of the family are ill (Folbre, 2014, Hudelson, 1996); increased susceptibility and negative health outcomes when pregnant (Khilnani, 2004, Mathad and Gupta, 2012, Sappenfield et al., 2013).

The influence of socioeconomic factors such as income and education, and socio-demographic characteristics such as age, ethnicity, marital status, place of residence, on health seeking, access and outcomes are well documented in the literature (Marmot et al., 2008, Sen, 2002, Prüss-Üstün, 2016). These are reflected in the social determinants of health (SDH), defined by the WHO as the conditions in which people are born, grow, live, work and age (Marmot et al., 2008).

Socio-demographic characteristics such as gender, income, education, geographical location, religion, race or ethnicity often interact in complex ways with systemic factors, to increase vulnerability and disadvantage – these interactions are particularly well examined through an equity of health access framework, and could offer policy-relevant analyses and recommendations (Oliver and Mossialos, 2004, Levesque et al., 2013, Levy and Sidel, 2013).

1.4. Understanding equity of access to healthcare

Health disparities do not refer to all health differences, but are specific to differences due to *intentional or unintentional discrimination or marginalization*, those *likely to reinforce social disadvantage and vulnerability* and relevant to social justice (Braveman et al., 2011) (p S150). They reflect social disadvantage due to positioning in a social hierarchy (Braveman et al., 2011). Health inequities can be perceived as being both systematic and social, and are perpetuated by social norms, policies and practices that facilitate unequal distribution of access to necessary social resources, including health systems and social determinants of health (Farmer et al., 2006, Marmot et al., 2008). Health equity does not refer only to differences in access to health services, as health is determined by a combination of genetics, behaviours, social and physical environment, as well as medical and public health services (Lalonde, 1974, Hayes and Delk, 2018).

Health equity, or fairness, is reflected in the absence of health differences that adversely affect socially disadvantaged groups (Goddard and Smith, 2001, Levy and Sidel, 2013, Braveman et al., 2011). Equity in healthcare access requires ensuring that every individual or group within a given population, irrespective of their socio-demographic characteristic or social position, has equal opportunity to access needed healthcare (Goddard and Smith, 2001, Levy and Sidel, 2013). There are three basic dimensions of equity in healthcare access: access to services based on needs, similar and appropriate health services for the same needs, and access irrespective of the socio-demographic characteristics of the individuals (Almgren, 2018, Goddard and Smith, 2001, Levy and Sidel, 2013). Equity of access may be measured in terms of the availability, utilisation or outcomes of services.

Access to healthcare is the ability to engage in timely use of the healthcare services that preserve or improve their health (Almgren, 2018, Gulliford et al., 2002). Access to healthcare is both opportunity and ability to obtain needed health services, without risking financial hardship (Evans et al., 2013). It can be defined as the possibility to identify needs, seek services, reach resources, obtain or use services, and be offered services appropriate to the needs of care (Levesque et al., 2013).

Although difficult to measure, equal access to healthcare is defined by equal opportunities to access and utilize healthcare for those in equal need, resulting in equitable health outcomes (Oliver and Mossialos, 2004, Musgrove, 1986). Using health system and individual-level data to identify areas of inequity, and with what factors it is associated, can be a more pragmatic approach than having a singular overall measure of how equitable a particular healthcare system is (Musgrove, 1986).

In their synthesis of several healthcare access definitions, Levesque et al articulate this as having two main dimensions: the accessibility of providers, organizations, institutions and systems (or supply) on one hand; and the ability of populations, communities, households and individuals (or demand) on the other (Levesque et al., 2013). For access to be achieved, services have to be available (potential access), and people have to be able to access them (realized access). Potential access is enabled by structural processes (availability and organization of health services and personnel), and patient socio-demographic characteristics (age, gender, marital status, income, education, geographic location) as well as perceived need and health beliefs. Realized access reflects utilization (numbers accessing care, referrals, loss to follow-up, adverse events and laboratory services) and satisfaction (convenience, affordability, and acceptability) (Andersen et al., 1983, Gold, 1998).

Timely access to DR-TB care, therefore, involves several components of healthcare access including availability and accessibility of health services, as well as acceptability and affordability for patients (Gulliford et al., 2002, Levesque et al., 2013).

1.5. Researcher background

My journey to a PhD started with two questions.

I worked for several years with the Institute of Human Virology, Nigeria (IHVN), an organization funded by the United States President's Emergency Plan for AIDS Relief and by the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM). The organization first received a grant to implement care for multi-drug resistant tuberculosis in 2011. Before this time, I had completed a Master of Public Health degree that explored access to treatment for HIV patients in a high prevalence State in Nigeria (Omenka, 2010). I was part of the program's health product supply chain team between 2011 and 2015, responsible for ensuring uninterrupted supply of critical anti-TB medications and working closely with the National TB and Leprosy Control Program (NTBLCP). I was also a part of the national, multidisciplinary team of experts responsible for the GFATM Phase II TB grant, the National TB Strategic plan and the GFATM application for the New Funding Model for HIV and TB.

Our team assessed facilities, expanded diagnostic and treatment services, delivered supplies, ensured a constant in-country drug supply of at least 6 months, monitored health products international pipelines, reviewed reports from individual treatment centers, and reported regularly to the GFATM team. During this time, I was puzzled by the high prevalence rates reported by the WHO and the consistent low numbers of patients the program was notifying and initiating on treatment, especially because these services were free. Despite the hard work put in by the country team in expanding services and ensuring adequate supplies, these were not leading to a commensurate surge in patient numbers. Was DR-TB incidence in Nigeria as high as was being reported by the WHO? What was stopping DR-TB patients from being diagnosed and accessing needed services? These questions, and the earlier research work on access to HIV treatment during my masters, led to a strong pull to do a study on access to DR-TB services in Nigeria.

This dissertation represents the results of five years of intensive work, including a two-month period spent in Nigeria in 2017. I worked with program managers in the National TB program and the Institute of Human Virology, Nigeria, the GFATM principal recipient for DR-TB implementation in Nigeria, to collect and analyze secondary diagnostic and treatment data, as well as qualitative interviews with program managers, providers, patients and their relatives.

1.6. Context of the study

Nigeria is a Federal Republic located in West Africa and covering 923,768 square kilometers. It is the most populous country in Africa, with an estimated population of 193 million people in 2016 (National Bureau of Statistics, 2017). It has 36 States, and the Federal Capital Territory (FCT) Abuja, and 774 local government areas (LGAs). The States are sub-divided into 6 geopolitical zones: North-East, North-West, North-Central, South-East, South-South and South-West (*Figure 1*).

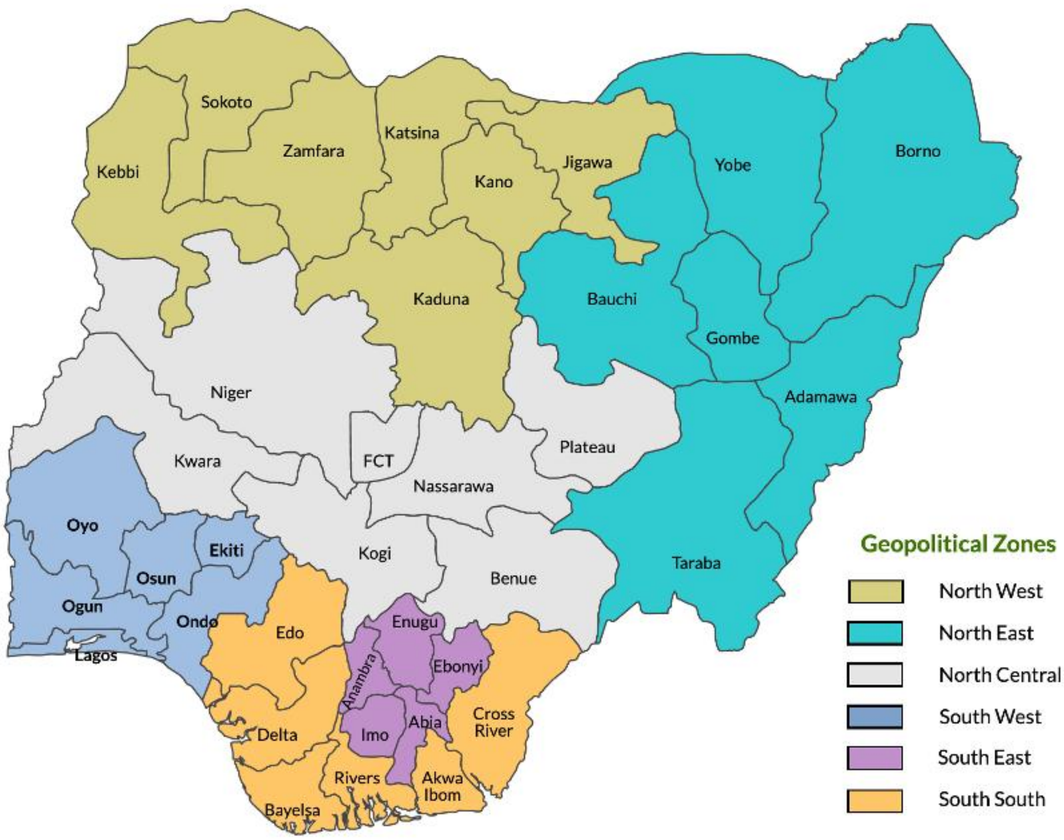


Figure 1. – Map of Nigeria showing six Geopolitical Zones

Nigeria's healthcare delivery is administered through the 3 tiers of government- federal, state and local governments. The Federal Government coordinates tertiary facilities (University Teaching Hospitals and Federal Medical Centres), the state governments focus on secondary healthcare (General hospitals) and the local government on primary healthcare (Asuzu, 2004). In 2017, the total expenditure on healthcare was 3.8% of GDP (Bank., 2017, WHO, 2017a). In the same year, 77.2% of all health expenditure were out-of-pocket, 14.2% funded by the government and 8.6% external aid; these rates have remained steady since 2011 (WHO, 2017a). Nigeria also has one of the highest percentage of out-of-pocket spending among high burden country as a fraction of total health expenditure (greater than 65%) leading to catastrophic costs for TB patients (WHO, 2019a).

Nigeria commenced free DR-TB treatment in 2010 with a hospital-based care model (8 months intensive phase in the hospital and 12 months continuation phase in the community) and adopted the use of Gene Xpert technology in 2011, leading to an increase in case detection. Treatment initiation for DRTB patients in the communities was piloted in 2013 (NTBLCP, 2014). However, as of 2018, only about 53% of notified DRTB cases were initiated on treatment (WHO, 2019a). Available literature does not clearly document how long DRTB patients are waiting to be started on treatment, nor the survival rates for patients who have been diagnosed but are not on treatment. This study contributes to filling this evidence gap

Nigeria has overlapping high burdens of TB, DR-TB and HIV, and ranks 6th in the world for people with TB and has an estimated 4.3% multi-drug resistance in new cases and 15% of previously treated TB patients. In 2018, there were an estimated 429, 000 TB cases out of which 21,000 were drug resistant. Out of these, 25% and 11% of TB and DR-TB cases were detected and notified[1](WHO, 2015c); and 24% and 9% of drug-susceptible and DR-TB cases/patients were placed on treatment, despite the fact that diagnosis and treatment has been free in the country since 2011 (WHO, 2019a, Ibrahim et al., 2014b, Ukwaja et al., 2013b). These are some of the lowest case detection and treatment rates in the world (WHO, 2019a). This highlights major difficulties in accessing TB diagnosis and treatment (WHO, 2016a, WHO, 2019a). Other studies found higher rates of DR-TB in Nigeria than previously estimated by the WHO, with Lagos being a hotspot for DR-TB infection in West Africa (Gehre et al., 2016, Onyedum et al., 2017). The National TB prevalence survey showed that the SW zone had the highest prevalence of TB and DR-TB (Gehre et al., 2016, Onyedum et al., 2017, FMOH, 2012b).

Since 2010, the Federal Ministry of Health has been providing free DR-TB care, with support from the Global Fund and other partners in 28 tertiary and secondary facilities within 27 States (NTBLCP, 2014).

1 TB case notification refers to the number of TB cases detected in a given year.

1.7. Statement of purpose, research questions and objectives

1.7.1 Statement of purpose

Low case notification has persisted in the Nigerian TB care system, and is even lower for drug-resistant TB detection (WHO, 2019a). Compared to drug-sensitive (DS-) TB, DR-TB has been noted in literature to be costlier and toxic, and more difficult for health systems to implement due to the additional technology and pre-treatment screening requirements. Few studies have explored the relationship between health system factors and patient socio-demographic characteristic with access to free DR-TB services in Nigeria (Oga-Omenka C, 2016), though a few have explored these factors in relation to drug-susceptible TB (Erah and Ojieabu, 2009, Okeibunor et al., 2007, Falzon et al., 2015, Ibrahim et al., 2014b). Timely diagnosis and treatment initiation reduces morbidity and mortality of TB disease as well as infection transmission (Dharmadhikari et al., 2014). This study focuses on access to DR-TB diagnosis and treatment in relation to patient socio-demographic characteristics and health system factors.

The purpose of this sequential transformative mixed methods study (Creswell et al., 2003) was to understand the health system and patient barriers and facilitators to DR-TB care access. The quantitative phase explored health system and patient factors associated with diagnosis and treatment, especially timely treatment initiation (within one month of diagnosis), as well as the gaps in the DR-TB care continuum. The qualitative phase enhanced the understanding of the health system and patient reasons for these gaps, as well as patient, treatment supporter and provider perspectives of access to the DR-TB care system.

1.7.2 Research questions

This study used quantitative and qualitative data to answer the following research questions:

1. What are the health system and patient factors that influence diagnosis and treatment for DR-TB in Nigeria?

2. What are the percentage dropouts and factors associated with attrition between each stage of the DR-TB care cascade?

3. Do the policies, structures and procedures for DR-TB support equitable diagnosis and treatment in Nigeria for different patient socio-demographic groups?

1.7.3 Objectives

1 To compare the socio-demographic characteristics between patients who are diagnosed and treated, with those who are diagnosed and untreated within the cohort of patients diagnosed with DR-TB in 2015;

2 To quantify gaps along the DR-TB continuum of care cascade, and highlight areas for improvements in access to care;

3 To qualitatively explore and describe reasons for socio-demographic differences in access to DR-TB care from the perspectives of healthcare providers, patients and their treatment supporters;

4 To describe health systems policies, structures and procedures for DR-TB diagnosis and treatment and how these relate to diagnosis and treatment for different patient socio-demographic groups using an equity of access to healthcare framework.

1.7.4 Hypotheses

1. There are barriers to treatment initiation and timeliness for DR-TB in Nigeria for certain marginalized groups of patients, including women, children and rural dwellers.

2. Gaps in DR-TB care cascade in Nigeria are influenced by patients' socio-demographic characteristics and healthcare factors;

3. Providers and patients' perspectives will offer some explanations for the quantitative data on barriers to DR-TB treatment initiation;

4. The policies, structures and processes for diagnosing and treating DRTB patients are not

equitable for all socio-demographic groups of patients.

1.8 Structure of this dissertation

This doctoral dissertation comprises six chapters, enumerated and summarized below.

Chapter 1 introduces and presents an overview of the study and the dissertation.

Chapter 2 introduces the theoretical framework guiding our study. It presents an adapted Levesque's patient centred access conceptual framework showing the interplay between patient pathway to accessing DR-TB healthcare and the care cascade in the context of the WHO health systems building blocks and the Andersen and Newman's individual determinants of healthcare utilization. Across the 6 articles included in this thesis (Chapters 3 to 6), the framework is applied at global, continental, national, and subnational levels.

Chapter 3 critically reviews the relevant literature in the form of two literature review articles. The first is a mixed method systematic review of evidence on provider and patient factors influencing access to DR-TB care in sub-Saharan Africa which was published in June 2020 in BMJ Global Health (Oga-Omenka et al., 2020c). The second article is a qualitative meta-synthesis of facilitators and barriers to tuberculosis care in Nigeria from 2006 to 2018, updated to include literature up to June 2020 and submitted to BMC Public Health in July 2020.

In chapter 4, I describe the mixed methodology used to undertake the empirical work presented in this thesis and explain how these methods help achieve the research objectives. The chapter also describes methods used to clean and link the diagnostic and treatment registers, the qualitative data collection methods, as well as the analysis performed and the ethical considerations.

The main dissertation results are presented in Chapter 5 in the form of three articles. The first article presents the results of a cohort analysis of patients diagnosed with DR-TB in 2015 in Nigeria and tracked into treatment. It was published in the PloSOne journal (April 2019) (Oga-Omenka et al., 2019). The second, focusing on the equity and ease of access of DR-TB services was submitted to the International Journal of Equity in Health in June 2020 (Oga-Omenka et al., 2020a). The third article uses the cascade of care framework to describe a 5-year trend and gaps in DR-TB care in Nigeria. This manuscript was submitted to the Journal of Clinical Tuberculosis and Other Mycobacterial Diseases (JCTUBE) in July 2020.

Chapter 6, which is the discussion and conclusion, synthesizes the main results, highlighting the major contributions. I also discuss the relevance of our conceptual framework and study limitations. The dissertation closes with a conclusion that links back to the objectives in the introduction. It includes the strengths and limitations of the study, as well as recommendations for practice and future research.

The dissertation closes with a Postscript, a commentary currently under revision for the journal Healthcare, on the challenges and opportunities which the COVID-19 pandemic, underway since early 2020, poses for tuberculosis control.

CHAPTER 2: CONCEPTUAL FRAMEWORK

2.1 Equity of access to healthcare

A conceptual framework helps to define the study, data to be collected and how these would be analysed (Miles and Huberman, 1994).

The predominant theoretical framework guiding our transformative study is the Levesque patient-centred access to healthcare framework, which is based on the concept of equity of access to healthcare (Goddard and Smith, 2001, Levy and Sidel, 2013, Levesque et al., 2013).

I chose the Levesque framework as our literature review identified an interplay of factors, both between the health system (supply) and patient (demand) levels, and at different stages of care. The framework also allowed us to explore some dimensions of the quality of care (patient-centred, equity, accessibility) (Corrigan, 2005, Kruk et al., 2016), which some authors have called the missing link in TB care (Kruk et al., 2016, Pai and Temesgen, 2019), without losing focus on the supply and demand dynamics of access.

The study data and findings were also considered through the lens of the TB continuum of care and cascade (Yang et al., 2014, Subbaraman et al., 2019b), the Behavioural Model (Andersen and Newman, 2005) and the WHO's health system building blocks (WHO, 2010b). These frameworks allowed us to further explore the dimensions of access identified in literature.

Equity in healthcare access focuses on ensuring equal access to and utilisation of healthcare for those in equal need, with equitable health outcomes (Oliver and Mossialos, 2004). Those with equal needs and equal opportunities do not always access healthcare equally. Reasons for this could be acceptable, if due to personal preferences, or unacceptable if due to unequal information or decision-making about healthcare (Oliver and Mossialos, 2004).

A transformative research design aims to ensure that the needs of marginalised populations are reflected at every stage. Transformative research advocates for social justice and addresses power imbalances using rigorous research (Creswell and Plano Clark, 2011, Sweetman et al., 2010, Mertens, 2007). This thesis uses a theoretical framework that is based on equity of access to healthcare, aimed at highlighting shortcomings in access to services based on needs, as well as similar and appropriate health services for the same needs, irrespective of the socio-demographic characteristics of the individuals (Goddard and Smith, 2001, Levy and Sidel, 2013, Levesque et al., 2013, Almgren, 2018).

Our framework builds on the above conceptualisations in patient-centred care, equity of access, quality of care, cascade of care, the human healthcare behaviour model and the health system building blocks, all of which have been used in numerous studies in these domains. Applying these to TB has the potential to focus attention on the gaps in and opportunities for better and more equitable access to high quality TB care, from testing through to occurrence-free survival. In future work, the framework could be strengthened with the inclusion of other aspects of quality of care like safety and efficiency (Corrigan, 2005, Kruk et al., 2016).

2.2 Dimensions of healthcare access

Using the Levesque framework as the foundation, we adapted the WHO health system building blocks and the Andersen individual and societal health behavior model to explore the DR-TB care cascade. These are discussed in more detail below.

2.2.1 DR-TB care cascade

In the context of DR-TB, the cascade of care concept brings a deeper understanding to the outputs needed from the health system to achieve DR-TB cure, once infected. Preventing gaps in the care cascade is also fundamental to the prevention of new TB infections, by increasing testing, diagnosis and treatment coverage. Increasing coverage for DR-TB care is a fundamental requirement to achieving the targets of the End TB Strategy (WHO, 2019a).

The concept of the care continuum, measured by the care cascade, was introduced to describe the spectrum of activities needed to be fully engaged in HIV clinical care, starting from symptom recognition, through health-seeking to being fully engaged in HIV care (Roscoe et al., 2020). It has been used successfully in relation to diseases or conditions requiring a series of procedures within the health system in order to achieve an outcome (Roscoe et al., 2020, Subbaraman et al., 2019b). Dropping out of this continuum of care has been associated with poor health outcomes across a spectrum of health issues, including TB (Roscoe et al., 2020, Scott et al., 2017, Price et al., 2018, Subbaraman et al., 2019b). This cascade of steps has been articulated for TB care to include symptom onset, presentation to the health facility, TB suspicion and testing, diagnosis, treatment and recurrence-free survival (Yang et al., 2014, Subbaraman et al., 2019b).

As the goal of the care cascade in TB is to achieve recurrence-free survival (Subbaraman et al., 2019b), and reduce transmission (WHO, 2019a), understanding how patient factors influence progression through the care cascade can offer providers and policy-makers much needed information on risk factors, health behaviors, or beliefs to improve services (Roscoe et al., 2020).

2.2.2 Health system building blocks

A health system consists of all the organizations, resources, actions and people whose primary purpose is to promote, restore, or maintain health (WHO, 2007). It delivers preventive, promotive, curative and rehabilitative actions at a personal or public health level, using State and non-State actors, and could be implemented at home, in the community or in a health facility (WHO, 2007, WHO, 2010b).

The health systems framework by the WHO presents the health system in terms of six building blocks to facilitate systems strengthening activities and promote health equity, while taking into account its multifaceted nature, spread of direct and indirect responsibilities, and intersection with multiple sectors. The building blocks include health service delivery, health workforce, health information management system, health products including vaccines and technologies, health financing, and health leadership and governance (WHO, 2007, WHO, 2010b). The WHO framework has been used effectively to assess health systems, monitor reforms and specific health problems (Manyazewal, 2017, Mounier-Jack et al., 2014, Percival et al., 2014, Tromp and Baltussen, 2012). However, some authors have noted the need to adapt the framework based on the specific need for each assessment, and to include issues of demand, power dynamics, process, and interactions between the blocks (Mounier-Jack et al., 2014, Huff-Rousselle, 2013).

2.2.3 Individual characteristics

Several theoretical frameworks have been proposed as a basis for understanding patient access barriers. Among these is the Behavioural Model by Andersen, which was later adapted into the Andersen and Newman's behavioral model of healthcare utilization (Andersen and Newman, 2005). This framework for health care access proposes that both individual and societal determinants influence health behavior and utilization. The model described these determinants as predisposing, enabling, and need factors (Andersen and Newman, 2005).

Predisposing factors are characteristics of the patient that exists before an illness (e.g. age, sex, gender norms, race, religion, and values concerning health and illness), that could also reflect the tendency, or *predisposition*, to use a particular healthcare service (Aday and Andersen, 1974). Enabling factors concern the "means" an individual has, within himself, his family or community, that *enables* them to use services (e.g., income, insurance coverage, rural/urban residence, region, travel means and time). The need factors refer to the degree of illness (perceived by themselves and or evaluated by health professionals); and this is what, results in the immediate health-seeking behavior and use of health service (Andersen and Newman, 2005, Aday and Andersen, 1974). These can be summarized as patient's sociodemographic and socioeconomic characteristics, health beliefs and need.

2.2.4 Patient-centred healthcare access

"Patient centered care" is defined as care that keeps the patient's preferences, needs, and values, at the centre of all clinical decisions, and is one of the six aims for high-quality health care (Committee on Quality of Health Care in America, 2001). It has been shown to reduce healthcare disparities and improve patients' well-being (Committee on Quality of Health Care in America, 2001).

Levesque et al (Levesque et al., 2013) puts the patients' needs at the centre of healthcare access framework, by focusing on the actual process of seeking care, including the various stages patients go through to actually receive needed care, and the abilities patients need to interact with health services (Levesque et al., 2013).

At its core, the Levesque framework conceptualizes accessibility in five dimensions: approachability, acceptability, availability, affordability, and appropriateness. These dimensions must be matched with five corresponding abilities in patients: ability to perceive, seek, reach, pay, and engage, respectively (Levesque et al., 2013).

2.3 The adapted conceptual framework

Based on an initial review of literature, we selected the Levesque framework as the foundation for our analysis. Over the course of the study, we iteratively included several other dimensions to the framework to help us further explore the patient and health system dynamics, as well as the cascade/continuum of care.

The adapted framework (*figure 2*) was used to frame the literature review, quantitative analysis, qualitative instruments and interpretations.

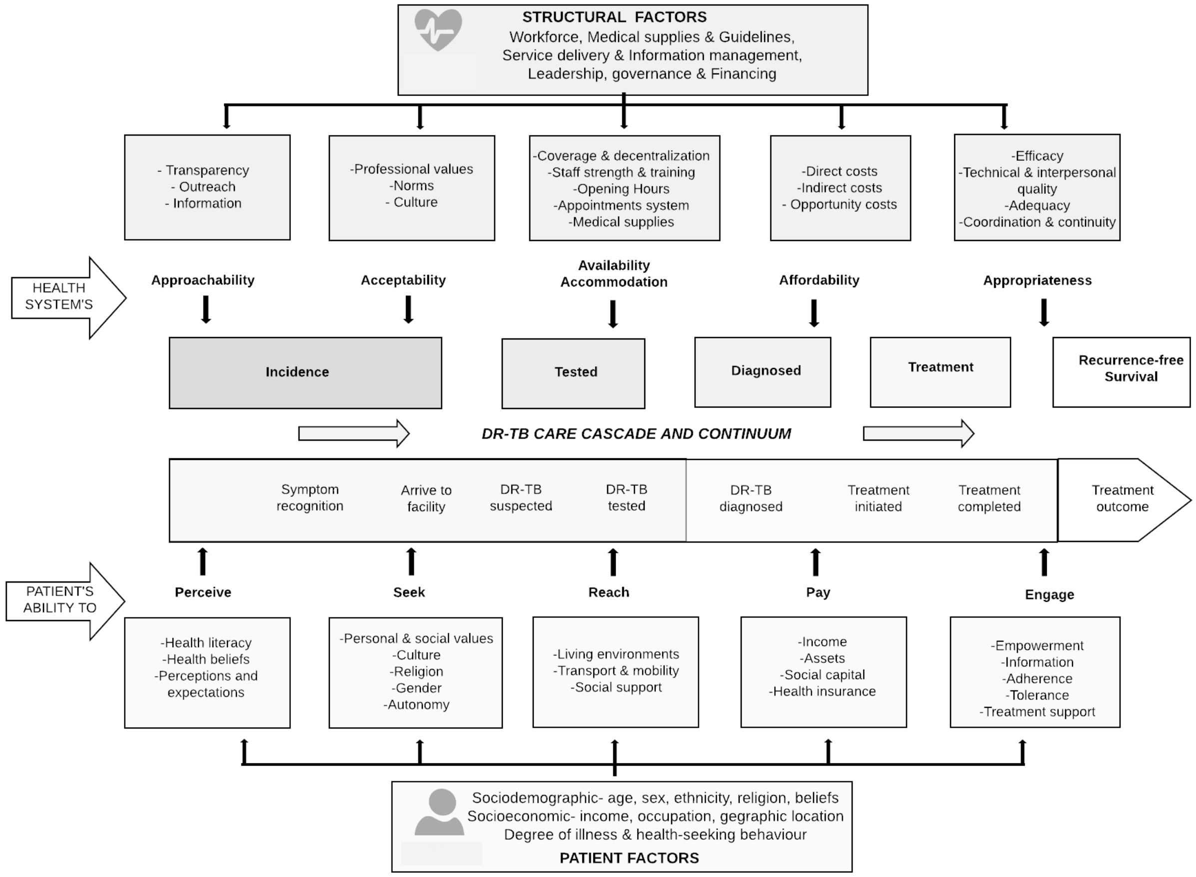


Figure 2. – An adapted framework of DR-TB care access

In the context of DR-TB care cascade, we understand these in the following steps:

At the time of becoming infected with DR-TB, each patient has certain predisposing characteristics that will impact where and how they seek a solution to their illness. A patient observes symptoms related to DR-TB disease and this triggers a number of actions based on their interpretation of the symptoms and their sociodemographic characteristics. At this point, they are unknown to the healthcare system and form part of the number of estimated incident cases.

Certain characteristics in themselves, and in the healthcare system, align at some point, and the patient recognizes that these symptoms require medical attention and that certain health services can be accessed. The health system enables this through public awareness, transparency and outreach services information. This is termed the approachability of health systems pairing with the patient's ability to perceive (Levesque et al., 2013). This stage ends with the patient deciding to seek care for their health problem.

For a patient to utilize healthcare, the health services need to be of acceptable and higher quality than other options available to the patient, as well as not violate any cultural, religious or social norms the patient might have. This would also need to align the patient's autonomy This is termed the acceptability of the health system aligning with the patient's ability to seek (Levesque et al., 2013). This stage ends with the patient choosing a particular health service over all other options.

To be able to reach the health service, it needs to be geographically available, with accessible opening hours and appointment systems. The patient needs to be able to transport to and reach these services. At the health facility, the patient needs to come in contact with a knowledgeable provider who suspects and tests for DR-TB. This would also need to align the patient's support system. The patient is now known to the health system and recorded as tested.

The next paired dimensions- affordability of health systems with patient's ability to pay – happen concurrently with the system's availability and the patient's ability to reach in order for diagnosis to take place. The direct and indirect costs of accessing care and the patient's socioeconomic situation determine whether a patient gets diagnosed and placed on treatment.

These costs and ability to keep paying for them will determine if the patient initiates and continues on treatment. The healthcare also needs to be efficacious, well-coordinated, uninterrupted and support the patient to be empowered and adhere to the treatment regimen to its completion. The patient also needs to be able to tolerate or withstand the effects of treatment and have adequate treatment support. Only then can the desired treatment outcome be achieved.

These healthcare and patient dimensions also need to build on each other and not change as the patient moves from one stage of the care cascade to the other. For example, treatment protocols need to be acceptable to the patient, and patients need to be able to have social support, autonomy and afford treatment right up to completion.

2.3.1 Application of the framework in this study

My primary objective for this study was to understand why DR-TB notification and treatment initiation rates in Nigeria were very low. I wanted to know if there were some barriers in the health system and at the patient level, and whether the intrinsic challenges of DR-TB treatment (costs to the health system and opportunity or other costs to patients, duration, toxicity) might result in a different pattern of facilitators and barriers to equitable access than for DS-TB. As such the systematic review, and qualitative interviews were focused on barriers up to the point of treatment initiation. In the cascade of care analysis, we also measure gaps in treatment completion. The interviews did not specifically probe for treatment completion. However, several patients still on treatment, their relatives, as well providers knew of patients who had interrupted or had died while on treatment. These factors were then reported specifically for treatment completion.

CHAPTER 3: LITERATURE REVIEW

Overview of literature review chapter

This chapter presents two literature review articles. We aimed to examine the TB access factors in both sub-Saharan Africa and specifically in Nigeria, as well as to compare the barriers that are both shared between drug-susceptible and drug-resistant TB or unique to DR-TB. We also wanted to see if a synthesis of qualitative data might offer additional insights into our research questions beyond the summary measures of technological and clinical intervention coverage.

The first article (Article 1) is a mixed methods systematic review. It aimed to identify barriers and facilitators influencing diagnosis and treatment for drug-resistant tuberculosis (DR-TB), which is necessary to develop effective strategies to find the missing incident cases and improve quality of care. We reviewed 29 studies from 6 sub-Saharan African countries- South Africa, Zimbabwe, Tanzania, Nigeria, Kenya and Gabon. This article was published in BMJ Global Health (July 2020).

The second article (Article 2) is a qualitative meta-synthesis of facilitators and barriers to tuberculosis diagnosis and treatment in Nigeria. It aimed to synthesize in-depth qualitative evidence on patients, community and health system factors influencing TB care in Nigeria. Ten studies were synthesized. It has been submitted to BMC Public Health.

The overall goal of the literature reviews was to highlight barriers and facilitators to DR-TB access identified by research in Africa, with the aim of shedding some light on the problem of low case detection in Nigeria. Case finding and treatment of active disease are proven strategies for controlling TB transmission and incidence and are international and national TB control goals. This study seeks to explore existing knowledge on these barriers from the African perspective with an aim to provide health workers and policy makers with a useful starting point for designing interventions targeted at improving case finding.

In Chapter 6, we come back to the literature review summary findings in relation to the research questions.

Article 1: Mixed Methods Systematic Review

Title page

Title: Factors Influencing Diagnosis and Treatment Initiation for Multidrug/Rifampicin Resistant Tuberculosis in six sub-Saharan African Countries: A mixed-methods systematic review

Corresponding author's name: Charity Oga-Omenka

Each author's affiliation and qualifications:

Charity Oga Omenka[1,2] B.Pharm, MPH, PhD(c.), Azhee Tseja-Akinrin[3] B.Pharm, MPH, Paulami Sen B.Sc[4,5], Muriel Mac-Seing[1,2] MSc(A.), PhD(c.), Aderonke Agbaje[6] MD, MPH, Dick Menzies[4,5] MD, Msc, Christina Zarowsky[1,2,7] MD, PhD

[1] École de santé publique de l'Université de Montréal (ESPUM), Canada

[2] Institut de recherche en santé publique de l'Université de Montréal (IRSPUM), Canada

[3] Azhee Akinrin Consulting, Nigeria

[4] Department of Epidemiology, Biostatistics and Occupational Health, McGill University

[5] McGill University International TB Centre, Montreal, Canada

[6] Institute of Human Virology, Nigeria

[7] School of Public Health, University of the Western Cape, South Africa

Keywords:

Access to healthcare, drug-resistant tuberculosis, mixed-methods systematic review, diagnosis and treatment, systematic review

Status: This article was published in BMJ Global Health in July 2020

DOI: http://dx.doi.org/10.1136/bmjgh-2019-002280

Abstract

Background

Drug-resistant tuberculosis burdens fragile health systems in sub-Saharan Africa, complicated by high prevalence of HIV. Several African countries reported large gaps between estimated incidence and diagnosed or treated cases. Our review aimed to identify barriers and facilitators influencing diagnosis and treatment for DR -TB in SSA, which is necessary to develop effective strategies to find the missing incident cases and improve quality of care.

Methods

Using an integrative design, we reviewed and narratively synthesized qualitative, quantitative and mixed method studies from nine electronic databases: Medline, Global Health, CINAHL, EMBASE, Scopus, Web of Science, IJTLD, PubMed and Google Scholar (January 2006 to June 2019).

Results

Of 3181 original studies identified, 55 full texts were screened, and 29 retained. The studies included were from 6 countries, mostly South Africa. Barriers and facilitators to DR-TB care were identified at the health system and patient levels. Predominant health system barriers were laboratory operational issues, provider knowledge and attitudes, and information management. Facilitators included GeneXpert MTB/RIF (Xpert) diagnosis and decentralization of services. At the patient level, predominant barriers were patients being lost to follow-up or dying due to lengthy diagnostic and treatment delays, negative public sector care perceptions, family, work or school commitments, and using private sector care. Some patient-level facilitators were HIV positivity and having more symptoms.

Conclusion

Case detection and treatment for DR -TB in SSA currently relies on individual patients presenting voluntarily to the hospital for care. Specific interventions targeting identified barriers may improve rates and timeliness of detection and treatment.

Summary Box

What is already known?

- Globally, only 39% and 32% of the estimated drug-resistant tuberculosis (DR-TB) patients are diagnosed started on appropriate treatment respectively.
- Ten high burden countries in Africa contributed 12% of the estimated global incident cases in 2018, with 54% of these in only Nigeria and South Africa.
- For patients who are diagnosed and placed on treatment, delays in access to diagnosis and treatment were up to several months in some sub-Saharan African countries.

What are the new findings?

- Laboratory operational challenges as well as inadequate healthcare worker knowledge, attitude and skills were the predominant barriers noted at the health system level.
- Predominant patient level barriers included loss to follow-up and death, as well inability to pay care-related costs.
- Availability of newer diagnostic tools was the predominant health-level facilitator of quicker diagnosis and treatment. However, this did not always translate to significantly higher rates of diagnosis and treatment.

What do the new findings imply?

- Implementers and policymakers need to better understand and address various issues that impact DR-TB care at different levels, in order to maximise the impact of new care innovations.

Introduction

Drug-resistant tuberculosis (DR-TB) is a major threat to global health as it undermines gains in TB control, and is especially burdensome to health systems in resource-limited settings (Gandhi et al., 2010a). Defined as TB resistant to both isoniazid and rifampicin, it is the leading cause of deaths due to antimicrobial resistance and took an estimated 214,000 lives in 2018 (WHO, 2019a). The 2018 United Nations (UN) High-Level resolution to 'end TB including DR-TB' by accelerating access to affordable prevention and care, is in line with earlier goals including the Sustainable Development Goals (SDGs) and The End TB Strategy (UN, 2018a, Osborn et al., 2015, WHO, 2015b). To meet these goals, it is essential to synthesise the growing evidence on barriers and facilitators to DR-TB care.

DR-TB is more difficult to diagnose and treat than drug-susceptible TB and is often associated with up to 5.5 times higher treatment costs, longer treatment courses and lower treatment success rates (Gandhi et al., 2010a, UN, 2018b, WHO, 2019a). Globally, only 39% and 32% of the estimated DR-TB patients diagnosed are started on appropriate treatment respectively (WHO, 2019a). Ten high burden countries (HBCs) in sub-Saharan Africa (SSA) contributed 12% of the 484,000 estimated incident cases in 2018, mostly in Nigeria and South Africa. Nigeria and Mozambique were among 10 countries contributing 75% of the global treatment enrolment gap (WHO, 2019a).

Gaps in TB care were notedly higher in Africa, where the Human Immunodeficiency Virus (HIV)-associated TB incidence is highest, as HIV further complicates TB care. Of 14 countries classified by the World Health Organization (WHO) as HBCs for TB, DR-TB and HIV, eight are in Africa (WHO, 2019a).

For DR-TB patients who are diagnosed and treated, several studies have reported delays in access running into several months in several SSA countries (Cox et al., 2015, Heller et al., 2010, Schaaf et al., 2003, Mpagama et al., 2013). These delays, occurring at patient and health system (provider) levels, contribute to increased morbidity, infection transmission, loss to follow-up, and poorer treatment outcomes (Dharmadhikari et al., 2014, Boyd et al., 2017). This review examines any synthesized qualitative and quantitative literature, with a view to inform policy and practice in SSA.

Our review question was ‘What are the patient or provider factors associated with delays in tuberculosis diagnosis and treatment in sub-Saharan Africa?’.

Methods

We used a mixed methods systematic review with an integrative approach(Whittemore and Knafl, 2005) to analyze data from qualitative, quantitative and mixed-methods literature and assessed quality using the *Consolidated criteria for reporting qualitative research* for qualitative studies (COREQ), *Strengthening the Reporting of Observational Studies in Epidemiology* - Combined tool (STROBE) and *Mixed Methods Appraisal Tool* (MMAT) tools, respectively (STROBE Statement, 2007, Tong et al., 2007, Hong et al., 2018).

We registered the systematic review protocol in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=106875).

Search strategy

Using a combination of key terms, we searched nine electronic databases: CINAHL, MEDLINE, Embase, Global Health, Scopus, Web of Science, International Journal of Tuberculosis and Lung Disease (IJTLD), PubMed and Google Scholar between January 2006 to June 2017, updating the search in June 2019. The year 2006 was used as this was the date of the first WHO publication guiding the programmatic management of drug-resistant tuberculosis.

The PICO (Population, Intervention, Comparator and Outcomes) framework (Moher et al., 2009) and key search terms used are summarized in *Supplementary file 1A*. The initial search terms were piloted and refined in CINAHL, and replicated in other databases, using appropriate strategies specific to each. The public health librarian at the University of Montreal’s School of Public Health validated this process.

Study selection and inclusion criteria

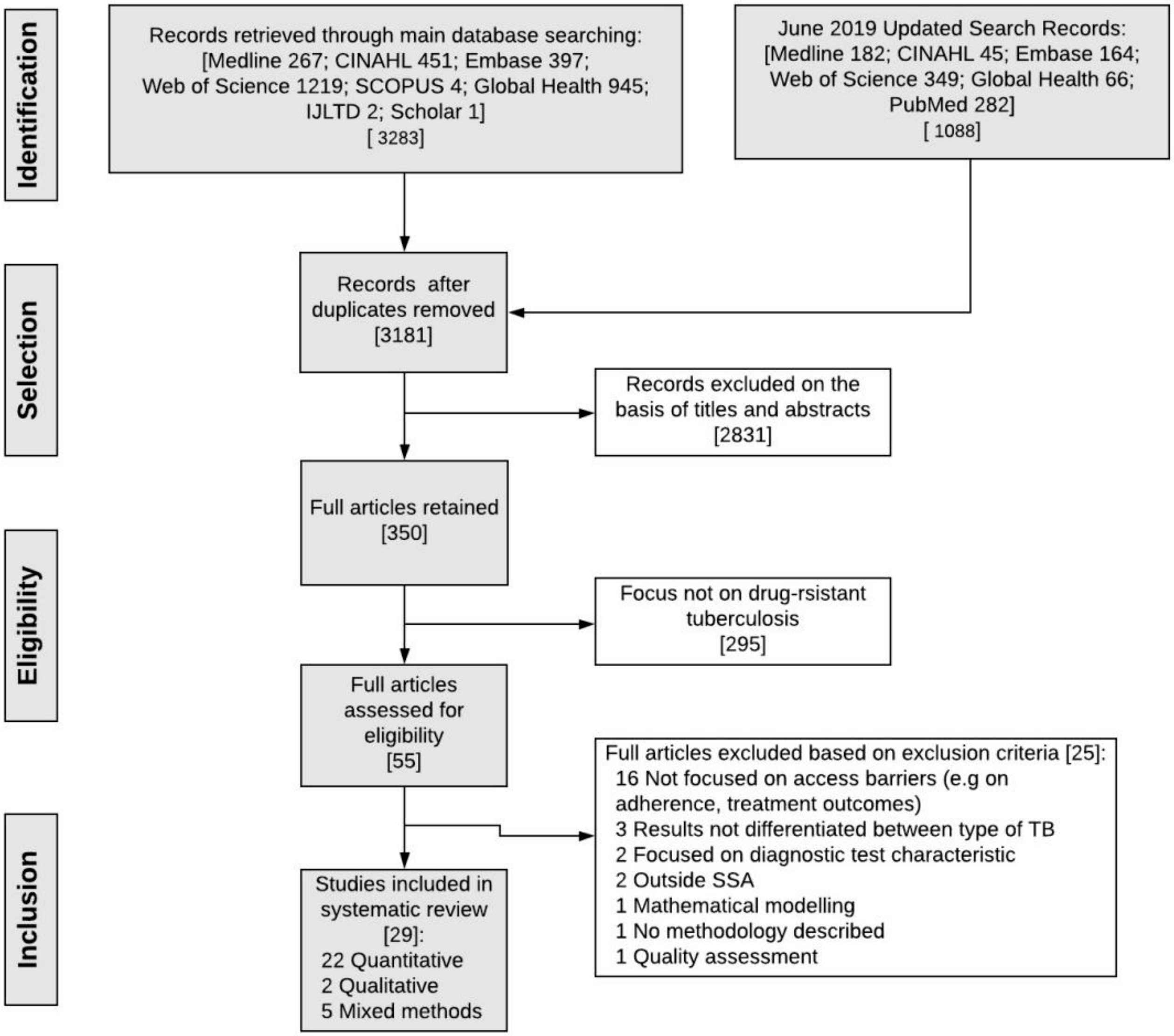


Figure 3. – Prisma Diagram of Study Selection

We selected studies (*Figure 3*) based on our inclusion criteria and PICO framework (*Supplementary file 1A*). Search results were downloaded into EndNote X7.7 and deduplicated. Titles and abstracts were screened, and full texts reviewed to determine studies for inclusion, and reasons for exclusion. All discrepancies or uncertainty were discussed and resolved by consensus during the final review.

Data extraction

Descriptive and analytical data were extracted (*Table 1*). Study findings and outcomes were grouped quantitatively and qualitatively (*Table 2*). Paired access dimensions and recommendations for some identified barriers, drawn from the studies themselves, were presented in the context of the Levesque's model of Healthcare Access (*Table 3*) (Levesque et al., 2013). Finally, a summary of access factors based on perceived importance and frequency of appearance (Clifford et al., 2018) are presented in *Supplementary file 1D*.

Quality assessment

We assessed the quality of studies through different critical quality appraisal tools based on study designs. Consensus was reached by discussion. For quantitative studies, we used the STROBE combined tool (STROBE Statement, 2007).The COREQ (Tong et al., 2007); and the MMAT was used to appraise mixed methods studies (Hong et al., 2018). The quality scores and assessment checklists are provided in *Supplementary file 1B and 1C*.

The overall quality assessments of "A" for high (>70%), "B" (50-69%) for medium, or "C" (<50%) for low were assigned based on independent evaluation by at least two reviewers for each study. The STROBE, COREQ and MMAT tools have been used in several systematic reviews as a basis for excluding low quality studies (Abegaz et al., 2017, Reeve et al., 2013, Pace et al., 2012).

Conceptual framework

We adapted a conceptual framework, mapping the TB care continuum from symptom onset to treatment initiation (Yang et al., 2014) to four corresponding dimensions of access at the provider and patient levels (Bailie et al., 2015, Levesque et al., 2013), and aligned these to identified barriers and facilitators from our review (*Figure 4*). We explained provider factors using the six health systems building blocks described by the WHO (WHO, 2007). Patient-level barriers and facilitators were described using the Andersen and Newman individual determinants of healthcare utilization (Andersen and Newman, 2005).

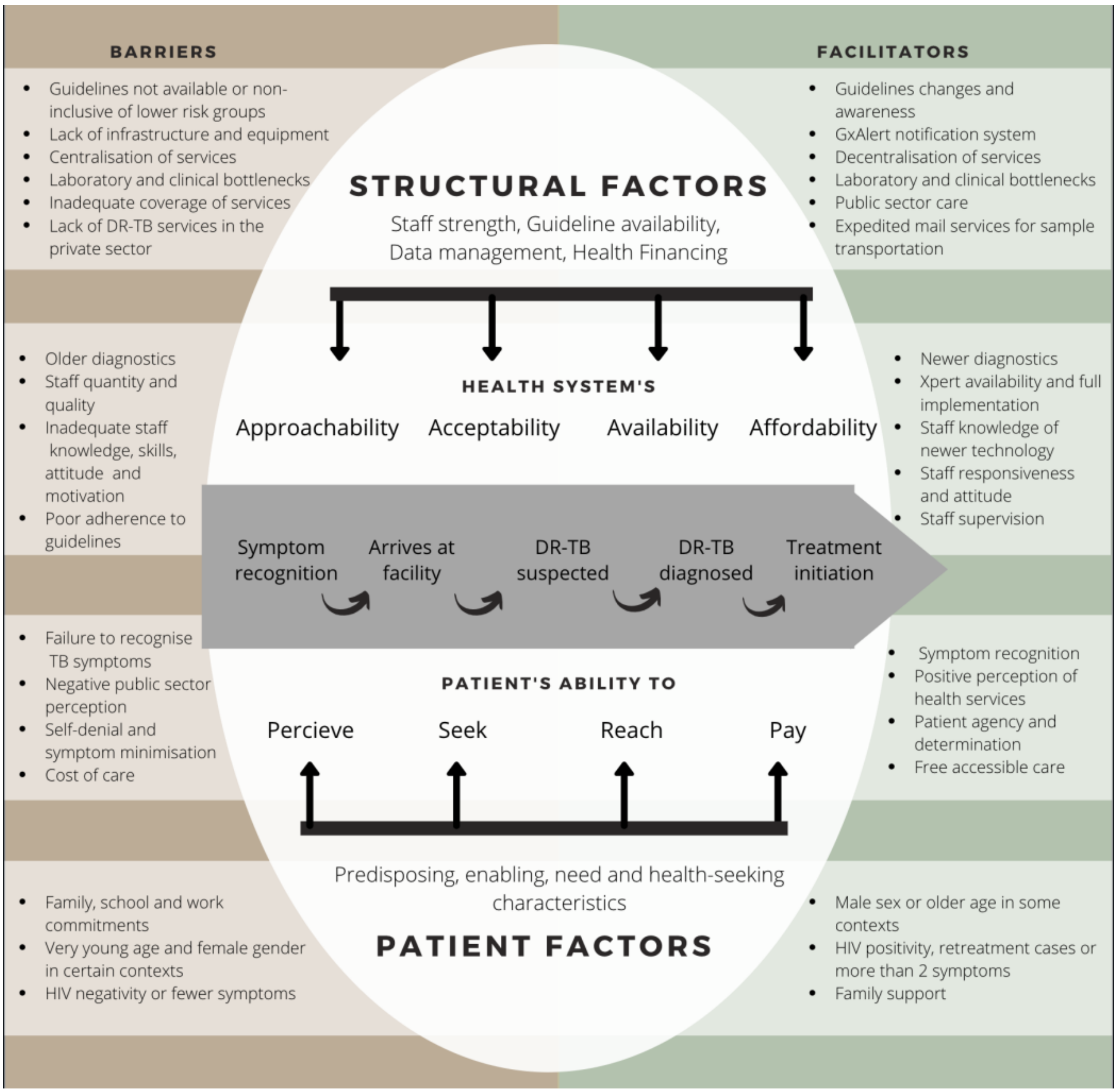


Figure 4. – An adapted conceptual framework of identified barriers and facilitators to DR-TB care.

Data analysis

We used an integrative approach (Whittemore and Knafl, 2005) to develop a narrative analysis of key findings from qualitative, quantitative and mixed methods studies, due to the high heterogeneity of selected studies. We repeatedly screened, coded and categorized data from each study in 4 ways: *Table 1* gives the selected study overview- first author and country, research design, population, intervention (when applicable), summary of barriers and facilitators, the level of care (diagnosis or treatment) in which they occurred, and the dimensions of care (provider or patient), the main findings and the quality assessment score.

In *Table 2*, we separated quantitative and qualitative findings for each identified factor. We reported associations that were statistically significant or relevant to our analysis and included representative quotes where available.

In *Table 3*, we used Levesque's model of healthcare access (Bailie et al., 2015, Levesque et al., 2013) to categorize data into 4 provider and patient paired dimensions: approachability/ability to perceive; acceptability/ability to seek; availability/ability to reach; affordability/ability to pay and finally appropriateness/ability to engage. The paired dimension of approachability and ability to perceive relates mostly to knowledge of providers and patients about services. Acceptability and the corresponding ability to seek focuses on cultural and social aspects that influence people's decisions to utilize health service and the personal autonomy and agency to make these decisions. Availability and the ability to reach refers to the physical existence of health systems and health workers, as well as the physical mobility and work flexibility of patients to reach available health resources. The dimensions of affordability and the corresponding ability to pay reflects the financial implications of health services and the capacity on the side of patients to bear these costs (Levesque et al., 2013).

To synthesize the factors identified across the variety of studies, we ranked each barrier and facilitator based on its importance within each study and the number of studies where it appeared *(Figure 5, Supplementary file 1D)*. A factor is assigned the maximum score of 3 if it affects >50% of participants or has an odds ratio of <0.65 or >1.5 for quantitative studies; and deemed as being of high importance or repeatedly mentioned across participant types. Factors are assigned a 2 if they affect 25-50% of participants, or odds ratio 0.65-0.8 or 1.25-1.5 for quantitative studies; or were deemed of moderate importance or by default when mentioned but not rated in qualitative studies. Factors were assigned 1 if affecting few participants and a zero if not mentioned. These scores were added for each study where the factor appeared. A similar method for synthesizing mixed methods reviews has been previously described (Clifford et al., 2018).

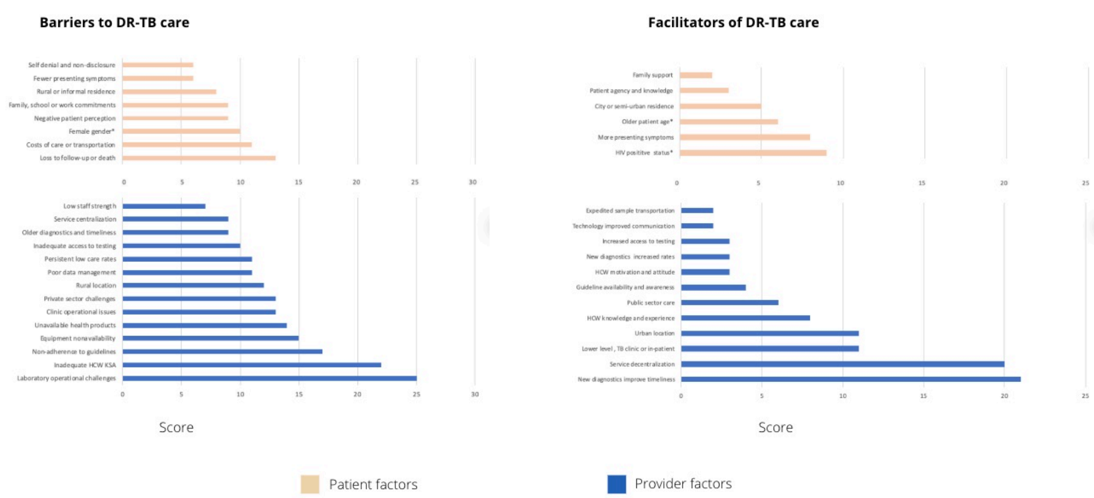


Fig 3: Summary of barriers and facilitators influencing DR-TB diagnosis and treatment in SSA, ranked both on frequency of appearance and perceived importance

Abbreviations: HCW- Healthcare worker; KSA - Knowledge, Attitude and Skills
*Inconclusive results; See *Table 2*

Figure 5. – Summary of access factors ranked both on frequency of appearance and perceived importance.

Patient and public involvement

Patients or members the public were not involved in this research.

Results

After an initial search yield of 3181 unique studies, 55 full texts met screening criteria, and a final selection of 29 articles were retained (*Figure 3*).

Study characteristics

The majority of the included studies were conducted in South Africa (n=20), with Zimbabwe (n=3), Tanzania (n=3), Nigeria (n=2), Kenya (n=1), and Gabon (n=1) making up the rest. These six countries represent 49.5% of the 77,000 estimated DR-TB incident cases in Africa in 2018 (WHO, 2019a). There were 3 qualitative, 22 quantitative and 5 mixed-methods studies. Among the quantitative studies, there were 13 retrospective, 3 prospective and 1 mixed cohort studies: and 5 cross-sectional surveys. All of the 3 qualitative studies employed in-depth interviews, with one study including focus group discussions (FGDs). Five studies examined access factors related to DR-TB treatment only, 9 on DR-TB diagnosis only, and 16 focused on both diagnosis and treatment. Factors impacting access were identified at provider (n=29) and patient (n=24) levels. Sixteen studies explored the influence of diagnostic tools on laboratory turn-around time (LTAT) and on treatment initiation. *Table 1* summarizes the study characteristics for this review.

Quality appraisal

The results of our quality assessment are shown in *Supplementary file 1B and 1C*. Out of a total of 22 quantitative studies, 20 were classified as A, with 2 scoring B based on the STROBE criteria (STROBE Statement, 2007). The two qualitative studies scored A and B using the COREQ tool (Tong et al., 2007), with one study, graded a C, excluded. Using the MMAT tool (Hong et al., 2018), 4 studies were graded A and one as B in mixed methodology.

Provider factors affecting DR-TB diagnosis and treatment

In all 29 retained studies, the most dominant factors affecting DR-TB care were provider-related (*Table 2, Figure 5*). Our study highlighted a wide range of specific problems reflecting nearly all aspects of service delivery and health workforce with a few issues related to leadership and governance, and management of health products and information.

Table 1: Overview of Selected Review Studies

Study ID Number	First author (Year) Country	Research design and methods Period	Populations (number)	Study objectives	Level of care (Diagnosis/ Treatment)	Dimensions of access	Summary of Findings	Assessment of study quality (score)
Qualitative Studies								
1	Bieh (2017) Nigeria	Qualitative FGDs, IDIs and KIIs May to Jul 2014	Patients (11) and health workers (4)	NA	Treatment	Structural and patient dimensions	Stigma and discrimination faced by patients and their care providers, as well as a lack of necessary tools in hospitals contribute to patient treatment delays.	B
2	Naidoo (2015) South Africa	Qualitative IDIs (part of a larger mixed method study including a retrospective cohort of 153 patients) 2010-2012	Patients (26)	NA	Diagnosis and Treatment	Structural and patient dimensions	Patients beliefs and knowledge of TB symptoms, as well as wrong perceptions of healthcare, and family commitments, compounded by health systems missed opportunities and delays, impact patients access to DR-TB care	A
Quantitative Studies								
3	Cox (2015) South Africa	Retrospective trend analysis Jan 2009 - June 2013	Patients (158)	The study compared Time to Treatment (TTT) of RR-diagnosed patients who were initiated on treatment before the decentralized program (2003–2006), during the first 2 years of the decentralized program, and full decentralized model of care	Diagnosis and Treatment	Structural dimensions	Decentralization of services and the introduction of Xpert were associated with significant reductions in TTI, after initial gains with the Line Probe Assay (LPA).	B
4	Cox (2017) South Africa	Retrospective cohort study 2011, 2013	Patients (2508 in 2011) (2528 in 2013)	Second-line treatment initiation and treatment delay were assessed among laboratory-diagnosed RR-TB patients before and after Xpert implementation.	Diagnosis and Treatment	Structural and patient dimensions	Patient characteristics like age and HIV status, as well as diagnostic precision and timeliness and other systemic barriers to delay access to diagnosis and treatment.	A

Study ID Number	First author	Research design and methods	Populations (number)	Study objectives	Level of care	Dimensions of access	Summary of Findings	Assessment of study

	(Year) Country	Period			(Diagnosis/ Treatment)			quality (score)
5	Dlamini-Mvelase (2014) South Africa	Retrospective cohort study Mar 2011 to Apr 2012	Patients (637)	This study assessed the availability of confirmatory DST and time to treatment of patients with Xpert diagnosed rifampicin resistance. Xpert results were compared with those of phenotypic and/genotypic drug susceptibility testing	Diagnosis	Structural dimensions	Poor adherence to the Gene Xpert algorithm especially with sending out confirmatory samples due to poor healthcare worker (HCW) training. The rollout of Xpert preceded the training of clinicians contributing to poor understanding of the lab algorithm for the diagnosis of DR TB.	A
6	Ebonwu (2013) South Africa	Cross sectional study Jan -Dec 2011	Patients (942)	Evaluation of treatment uptake and loss to follow up of newly diagnosed MDR-TB patients and the proportion of patients who remained on treatment after initiation.	Treatment	Structural and patient dimensions	Referral for laboratory diagnosis from hospitals, some health districts, HIV- and township place of residence were associated with non-initiation of MDR-TB treatment.	A
7	Evans et al. (2018) South Africa	Retrospective cohort study: Early cohort: Jul 2011 to Jun 2012 (35% or limited Xpert implementation) Late cohort: Jul 2013 to Jun 2014 (>90% Xpert implementation)	Patients: Early cohort (594) Later cohort 713	Study compared treatment initiation and time to treatment of adult patients with laboratory-confirmed RR-TB in Johannesburg 2011-2012 (early cohort) vs 2013-2014 (late cohort).	Diagnosis and Treatment	Structural and patient dimensions	The implementation on Xpert has increased diagnostic capacity and initiation of treatment of patients, but inherent patient barriers such as HIV status, drug resistant TB disease, as well as high rates of loss to follow up impede treatment success rates.	A
8	Hanrahan et al. (2012) South Afria	Observational cohort study: Aug 2007-Jan 2008 with MGIT phenotypic DST testing Oct 2009-Mar 2010 with LPA testing	Patients (n=1176 for before) and (n=1177 for after)	'Before and after'' cohort study comparing data on adult pulmonary TB patients registered at public health clinics before and after the 2009 introduction of an expanded DST algorithm using MTBDRplus version 1.0	Diagnosis and Treatment	Structural and patient dimensions	Introducing the faster LPA DST testing cut down time to diagnosis and increased RR-TB case detection without the expected impact on TTI due to other bottlenecks in the HS, particularly required hospitalization.	A
9	Hanrahan (2013) South Africa	Prospective cohort study Jul to Sep 2011	Patients (641)	The study evaluated the diagnostic follow-up, clinical characteristics and outcomes of a cohort of tuberculosis suspects screened using a single point-of-care Xpert.	Diagnosis and Treatment	Structural and patient dimensions	* Point-of-care Xpert provided quicker treatment initiation. * Almost all TB suspects testing Xpert-positive were started on TB treatment the same day as presenting with TB symptoms. This was two weeks faster than Xpert-negative suspects who started empirically or based on suggestive chest x-ray, and 20 weeks faster than those diagnosed by culture.	A

Study ID Number	First author (Year) Country	Research design and methods Period	Populations (number)	Study objectives	Level of care (Diagnosis/ Treatment)	Dimensions of access	Summary of Findings	Assessment of study quality (score)
10	Iruedo (2017) South Africa	Retrospective cohort study Jan 2009 to Dec 2014	Patients (342)	This study analysed the medical records of patients diagnosed with MDR-TB , comparing diagnostic modalities to assess the effect of Xpert on time to treatment	Diagnosis and Treatment	Structural and patient dimensions	Xpert significantly reduced the time to DR-TB diagnosis and consequently a reduction in TTTI. This was significantly shorter with Xpert compared to LPA and culture/phenotypic DST	A
11	Jacobson (2012) South Africa	Retrospective cohort study 2007-2011	Patients (197)	Study compared records of patients tested using the MTBDRplus test and patients tested with culture-based DST to determine whether implementation of the rapid MTBDRplus diagnostic shortened the time from specimen collection to initiation of treatment.	Diagnosis and Treatment	Structural and patient dimensions	The use of line probe assay (LPA) for diagnosis dramatically improved TTI but laboratory and clinical operational delays still a problem.	A
12	Jacobson et al. (2017) South Africa	* Retrospective cohort in Western Cape: 2 samples collected at baseline- 1 for Xpert and 1 for LPA and culture-based DST Nov 2011 – Jun 2013 * Prospective cohort in 3 other provinces: 1 sample collected at baseline for Xpert; a subsequent one for LPA and culture-based DST only where RR-TB is diagnosed on the first specimen. Nov 2012 to Dec 2013	Patients (1332) * Western Cape Province: (835) * Eastern Cape, Free State, and Gauteng Province: (497)	Study quantified the time to second-line DST results and proportion of patients potentially placed on suboptimal therapy by evaluating records of patients diagnosed with RIF-resistant tuberculosis by Xpert.	Diagnosis and Treatment	Structural and patient dimensions	* Incomplete and decreasing adherence to National requirements for DST, due to a variety o reasons, impedes patients' diagnosis; * Long turnaround time for DST results of 53 days following RR-TB diagnosis exposed many patients to ineffective therapies.	A
13	Jokwiro et al. (2018) Zimbabwe	Cross-sectional study. Jan 2016 – Jun 2017 with 2 phases: * Xpert only for presumptive DR-TB and HIV coinfection: Jan – Jun 2016 * Xpert recommended for all patients with presumptive DR-TB: Jan – June 2017	Assays done in 1 provincial, 6 district and 6 rural hospitals. 13 Xpert assay instruments (13137 total assays): *2016: (4556) *2017: (8581)	Compared the utilisation and results of deploying Xpert when recommended only for those with presumptive DR-TB and HIV coinfection vs when Xpert was recommended for all presumptive TB patients.	Diagnosis	Structural dimensions	* Increased access to Xpert utilization beyond high-risk groups slightly increased the detection of drug susceptible, but not DR-TB strains among patients. * Persistent HS challenges impede utilization of Xpert for TB diagnosis.	A

Study ID Number	First author (Year) Country	Research design and methods Period	Populations (number)	Study objectives	Level of care (Diagnosis/ Treatment)	Dimensions of access	Summary of Findings	Assessment of study quality (score)
14	Kweza (2018) South Africa	Cross sectional survey Mar to Dec 2015	Patients (1255)	Estimated the proportion of TB patients missed by primary health clinics using interviews and testing TB-symptomatic patients in 20 randomly selected PHCs in South Africa	Diagnosis	Structural and patient dimensions	Patients were not screened for TB even when presenting with symptoms. HS missed most TB patients attending PHCs for TB- related symptoms and for other reasons.	A
15	McLaren (2017) South Africa	Health care evaluation 2004-2011	Tests (26,245,412 in 429 hospitals)	The study assessed quality of care in public health facilities in South Africa by analyzing data extracted from the South African National Health Laboratory Service (NHLS) database for TB tests performed in public health facilities	Diagnosis	Structural and patient dimensions	* Facility not adhering to national standards of care. Not all patients with TB provided a second specimen for testing, even fewer received follow-up testing or DST. However, DST rates improved steadily over time. * Effect of policy and guideline changes on testing rates shown to be transient	B
16	Metcalfe et al. (2016) Zimbabwe	Prospective study: November 2011 – June 2014	Patients (352)	Diagnostic accuracy for rifampin-resistance and time to second-line regimens were ascertained by comparing TB testing done with Xpert to solid and liquid culture, and DST of outpatients with history of prior tuberculosis.	Diagnosis and Treatment	Structural and patient dimensions	Rapid diagnosis with Xpert was not, in itself, enough to remove health system delays to treatment initiation.	A
17	Mohr (2017) South Africa	Retrospective cohort study Jan 2012- Dec 2014	Patients (543)	The study analyzed medical records of patients diagnosed with RR-TB to assess the proportion of RR-TB patients with potential to have been diagnosed earlier	Diagnosis	Structural dimensions	Lack of guideline adherence leads to patients not being diagnosed	A
18	Moyo et al. (2015) South Africa	Retrospective analysis study: 2008-2013	Adolescent patients (71)	An analysis of data for adolescents aged 10-19 years who were diagnosed with DR-TB was conducted to describe frequency of patient outcomes, particularly treatment success, treatment failure, loss to follow up and deaths	Treatment	Structural and patient dimensions	Treatment refusal and loss to follow up were the predominant reasons for non-initiation of treatment.	A

Study ID Number	First author (Year) Country	Research design and methods Period	Populations (number)	Study objectives	Level of care (Diagnosis/ Treatment)	Dimensions of access	Summary of Findings	Assessment of study quality (score)
19	Naidoo (2014) South Africa	Observational analysis of 10 facilities Jan 2008 to Dec 2012	Patients (541)	Study compared MDR-TB treatment commencement times in MDRTBPlus Line Probe Assay vs Xpert-based algorithms in a routine operational setting.	Diagnosis and Treatment	Structural and patient dimensions	* Xpert reduced TTI by eliminating lab turnaround time. However, patients still being delyed by other steps needed before treatment initiation. * There were no indications that patient age or sex were relevant in TTI.	A
20	Nkosi (2013) South Africa	Cross sectional survey 2008	Patients (148)	To determined reasons for non-referral of MDR-TB and XDR-TB cases, this study administered questionnaires to provincial primary health care facilities and hospitals providing routine care for TB	Treatment	Structural and patient dimensions	Poor HCW knowledge of the national DR-TB guide- lines contributing to non-referral for DR-TB care. Patients were also s lost to follow up or did not return for results.	A
21	Oga-Omenka et al. (2019) Nigeria	Retrospective cohort study. Jan 2015- August 2017	Patients (996)	Study examined rate and timeliness of TTI using 2015 diagnosis and treatment data from the Nigerian TB program electronic records. It also compared health system and patient characteristics	Treatment	Structural and patient dimensions	Geographic location as well as level of healthcare facility influenced patient treatment initiation within an appropriate timeframe, as recommended by the National guideline.	A
22	Oliwa et al. (2018) Kenya	Cross-sectional study: 2015	Patients (82 313)	Study used 2015 Kenya National TB program data to map TB case notification rates (CNR), and capacity to perform diagnostic tests (chest x-rays, smear microscopy, Xpert culture and LPA.	Diagnosis	Structural and patient dimensions	Despite guideline specifications, Xpert use was sub-optimal, negatively affecting diagnosis, especially in children and other lower risk individuals- HIV-, well-nourished patients.	A
23	Timire et al. (2019) Zimbabwe	Cohort study April 2017 –April 2018	Patients (133)	Study determined the impact of the Hain technology (timeliness and proportion of DST tests among RR-TB cases) by analyzing facility laboratory registers.	Diagnosis and Treatment	Structural and patient dimensions	While decentralization and access to RR-TB treatment positively impacted timely initiation of standard treatment, distance from the NRL hindered timely collection and return of DST.	A
24	Van Den Handel (2015) South Africa	Prospective evaluation using 3 different diagnostic approaches Apr 2011 to Dec 2013	Patients (1449)	The impact of Xpert and decentralization on patient care in sparsely populated areas with poor access to laboratory and radiology services was determined by comparing three diagnostic approaches: Centralized smear microscopy, and Centralized or Decentralized Xpert	Diagnosis	Structural dimensions	* Xpert introduction did not significantly increase rates of detection; However, more diagnosed cases initiated treatment and quicker. * Decentralized Xpert enabled same-day treatment for most patients, and eliminated the time to treatment compared to the centralized Xpert.	A

Study ID Number	First author (Year) Country	Research design and methods Period	Populations (number)	Study objectives	Level of care (Diagnosis/ Treatment)	Dimensions of access	Summary of Findings	Assessment of study quality (score)
Mixed Methods Studies								
25	Doulla et al. (2019) Tanzania	Qualitative FGDs, IDIs: 2012 Quantitative cross-sectional sample analysis: Jan 2011 to Dec 2013	Qualitative 45 Healthcare workers (HCW) Quantitative 2,759 samples	The effectiveness and stakeholder perception of routine surveillance system for previously treated tuberculosis cases was evaluated through in-depth interviews and focus group discussions with health care providers. Also, quantitative data were extracted from the routine databases	Diagnosis	Structural dimensions	Barriers: Inadequate management of specimens, lack of resources, and work inconsistencies from staff (e.g. delay, miscommunication, inconsistent training etc.) lead to poor diagnosis and leave room for diagnostic delay. Facilitators: District support and mailing system is beneficial if properly in place.	A
26	Mpagama et al. (2019) Tanzania	Retrospective cohort study and Cross-sectional study: 2015	28 TB districts 399 Patients	Study identified healthcare system related barriers to implementation of molecular diagnostics for MDR-TB by interviewing relevant stakeholders and auditing registers of drug-susceptible re-treatment TB cases and TB collaborative practices in HIV clinics	Diagnosis and Treatment	Structural and patient dimensions	Overall, underdiagnoses of MDR-TB occurred in a region where drug resistance is expected to be prevalent. HCWs lacked the tools, expertise and knowledge to appropriately manage TB patients. This impaired timely MDR TB treatment initiation among patients.	B
27	Mnyambwa et al. (2018) Tanzania	Retrospective cohort study: January 2013 - September 2016 Qualitative: In depth interviews with Key Informants	Chart review: Patients (782) Qualitative interviews: TB coordinators (27)	A retrospective review of patients' clinical data and subsequent in-depth interviews with health providers were conducted to assess the effectiveness of the GeneXpert GxAlert platform for MDR-TB diagnosis and its impact on linkage of patients to care in Tanzania.	Diagnosis and Treatment	Structural and patient dimensions	Although the GeneXpert GxAlert platform fulfilled its task, inconsistencies within the healthcare framework itself including the work of its professionals ultimately prevent correct management of patients.	B
28	Westhuizen et al. (2017) South Africa	Cross-sectional study: 2015	Medical students (12)	A self-administered questionnaire and interviews were administered to current medical students and recently graduated doctors in Cape Town to determine the frequency and impact of occupational TB disease.	Diagnosis and Treatment	Structural and patient dimensions	Overall, medical students do not have proper access to support as well as services in order to be appropriately treated.	B
29	Zimri (2012) South Africa	Qualitative FGDs and Quantitative case control (CC) Aug to Sep 2011	FGD of 10 parents/care givers Case control: 50 patients in each arm (100)	FGDs and questionnaires were administered to caregivers of children referred to a specialist pediatric MDRTB clinic in Cape Town to determine why many child contacts of MDR-TB are not brought for assessment, despite local policy advise.	Diagnosis	Structural and patient dimensions	HCW attitude, coloured ethnicity, the mother being the source case, having a smoker resident in the house, difficult transport- time , cost and number of transitions required to get to the specialist clinic, and fear of infection whilst waiting to be seen were some barriers identified in the study	A

Abbreviations: IDI- In-depth interviews; FGDs - Focus group discussions; KIIs- Key informant interviews; HCW- Healthcare worker; HS= health system; TTI-Time to treatment initiation; SL- Second line; MGIT- Mycobacteria Growth Indicator Tube; NRL- National or Central Reference Laboratory; d-days; TB- Tuberculosis; RR-TB- Rif-resistant TB; DR-TB- Drug resistant TB; Xpert- GeneXpert MTB/RIF Assay; LPA- Line Probe Assay; DST- culture/phenotypic drug sensitivity testing; RR- Risk Ratio; NE-North East; SE-SouthEast; SW- SouthWest

Service delivery was, by far, the most predominant provider-related barrier. Laboratory (Jacobson et al., 2017, Mpagama et al., 2013, Doulla et al., 2019, van der Westhuizen and Dramowski, 2017, Timire et al., 2019, Mnyambwa et al., 2018, Naidoo et al., 2015a) and clinic (Doulla et al., 2019, Mpagama et al., 2013, Oga-Omenka et al., 2019, Mohr et al., 2017, Mnyambwa et al., 2018) operational challenges, as well centralization of services (Cox et al., 2015, Evans et al., 2018, Moyo et al., 2014, Timire et al., 2019, Van Den Handel et al., 2015, Hanrahan et al., 2013, Naidoo et al., 2015a, Naidoo et al., 2014b, Doulla et al., 2019) and poor linkage between the public and private sector (van der Westhuizen and Dramowski, 2017, Naidoo et al., 2015a), hampered care. Inadequate provider knowledge, skill and adherence to national guidelines were also recurring themes (Doulla et al., 2019, Mpagama et al., 2013, Zimri et al., 2012, van der Westhuizen and Dramowski, 2017, Dlamini-Mvelase et al., 2014, Naidoo et al., 2015a, Nkosi et al., 2013, Cox et al., 2017, Jacobson et al., 2017, Mohr et al., 2017, Oliwa et al., 2018, Timire et al., 2019). These are discussed in more detail in the context of the paired dimensions of access.

Patient-level factors influencing DR-TB diagnosis and treatment

Most patient-level barriers were related to predisposing characteristics including knowledge and perceptions (Naidoo et al., 2014b, Zimri et al., 2012, van der Westhuizen and Dramowski, 2017, Bieh et al., 2017b), HIV status (Hanrahan et al., 2013, Oliwa et al., 2018, Cox et al., 2015, Cox et al., 2017), presenting symptoms (Kweza et al., 2018, Oliwa et al., 2018), gender (Kweza et al., 2018, Oliwa et al., 2018) and age (Kweza et al., 2018, Oliwa et al., 2018, Cox et al., 2017, Jacobson et al., 2017); and enabling characteristics including geographic location (Jacobson et al., 2017, McLaren et al., 2017, Metcalfe et al., 2016, Timire et al., 2019, Mpagama et al., 2013, Cox et al., 2017, Jokwiro et al., 2018, Doulla et al., 2019), life commitments (Zimri et al., 2012, van der Westhuizen and Dramowski, 2017, Naidoo et al., 2015a), and the ability to pay for transportation or services (Zimri et al., 2012, Naidoo et al., 2015a, Naidoo et al., 2014b, van der Westhuizen and Dramowski, 2017). A few need and health-seeking characteristics were also identified relating to treatment refusal (Moyo et al., 2014), choosing private sector care (Naidoo et al., 2015a, Mpagama et al., 2013).

Paired Access Dimensions

We have summarized access factors and recommendations from the reviewed studies into four paired dimensions (*Table 3)* (Levesque et al., 2013).

Approachability/ability to perceive

We found that provider and patient knowledge about DR-TB services (Levesque et al., 2013) were hindered by inadequate leadership and governance, provider training, service delivery, patients' predisposing and need characteristics (Levesque et al., 2013, Andersen and Newman, 2005, WHO, 2007). At the systems level, inadequate patient tracking, referrals, and follow-up, poor provider knowledge about the service requirements, and inadequate guideline availability and non-adherence were identified challenges (Cox et al., 2017, Ebonwu et al., 2013, Nkosi et al., 2013, Mohr et al., 2017, Kweza et al., 2018, Dlamini-Mvelase et al., 2014, Evans et al., 2018, Doulla et al., 2019, Mpagama et al., 2013, Mnyambwa et al., 2018, Zimri et al., 2012, Naidoo et al., 2015a). Patients' ability to perceive the right services were hampered by health illiteracy, poor perceptions of services and distrust and unmet expectations (Naidoo et al., 2014b, Zimri et al., 2012, Mnyambwa et al., 2018).

At the health systems level, the consequences of poor leadership and governance were reflected in patient nonreferral, misdiagnosis and treatment with ineffective regimens (Nkosi et al., 2013, Naidoo et al., 2015a). Guidelines awareness, availability and expansion to include low risk groups were shown to improve access (Hanrahan et al., 2012, McLaren et al., 2017, Nkosi et al., 2013, Naidoo et al., 2015a).

Table 2: Quantitative and Qualitative Findings

Factor	Quantitative findings 95% CI [study ID]		Qualitative findings [study ID]	
	Barrier	Facilitator	Barrier	Facilitator
Healthcare system level barriers (based on the WHO Health Systems Framework)				
Leadership and governance				
Guidelines availability and inclusion of low risk groups	* Patient referral hampered as most PHC and hospital HCW were unaware of the national DR-TB guidelines [20]	* Testing rates were transiently responsive to changes in clinical guidelines and with awareness campaigns/conferences [15] * Implementation of the expanded algorithm resulted in a dramatic increase in the application of DST among new cases and a substantial increase in the rates of diagnosis [8]		
Service delivery				
Infrastructure and equipment	* Xpert and chest X-ray were unevenly distributed, irrespective of TB burden 22] * Few selected districts had laboratories with capacity for performing molecular diagnostics resulting in more specimens received than processed per day throughout the regions [28] * Non-functional Xpert machines reported, varying by region, reducing testing capacity [26]	* The GxAlert notification system sending short texts messages to TB Coordinators when a MDR-TB case was detected. The coordinators also communicated this info with the respective district coordinators [27]	* Lack of necessary infrastructure and tools [1, 25] * HCW blamed for lack of equipment and delays [1] *"Sometimes they take it out on the health workers because, they are the people they see. If there is any form of dissatisfaction with service, if there is a power outage, of course they take it out on you and its very painful... you are not providing power, you are making us uncomfortable" [1]*. * Unreliable equipment maintenance and electrical fluctuations noted as a challenge to DR-TB care [26]	
Decentralization and integration	* Persistent treatment preparation delays remained even with Xpert use due to centralized implementation of pre-MDR-TB treatment clinical requirements like X-ray & liver function tests, audiometry [19]	* Decentralization during 2008–2011 was associated with declining TTT [9]. * Decentralized (outpatient) sites showed significantly higher treatment initiation rates compared to centralized, inpatient sites [7]. * Decentralization, Xpert implementation and the corresponding reduction in TTI was associated with improved adolescent patient outcomes [18]. * Decentralization and accessibility to RR-TB treatment facilitated access to standard treatment for most diagnosed patients [23] * Decentralized Gene Xpert eliminated lab diagnosis time and improved overall rates of diagnosis. [24]	* A lack in integration resulted in shortage of materials [25] *"Our programme is vertical, so when there is a shortage of slides we grieve, they should integrate so that some of these things could also be budgeted for ..." [25]"*	* Available, decentralized DR-TB treatment a facilitator to early care [2]

Factor	Quantitative finding 95% CI [study ID] Barrier	Quantitative finding Facilitator	Qualitative finding [study ID] Barrier	Qualitative finding Facilitator
Service delivery				
Laboratory operational issues: sputum transportation, turn-around time, testing rates, communication and linkage to care	* Reasons for DST not done were contamination, failure to grow on culture /loss of viability or DST not performed [12] * Laboratory operational issues resulted in only half of DST results performed, even though sputum was collected from most RR-TB diagnosed patients, most of which reached the NRL; Even fewer got back to the peripheral facilities [23]. * Only 32.4% of previously treated cases notified were received at the NRL in 3 years. 57.6% and 97.2% of culture and DST test had laboratory turn time longer than recommended [25] * 25% of submitted specimens did not have results communicated back to the clinic including for 18% of tests performed in PLWH [26] * Only 32.3% of new RR-TB cases notified were placed on DR-TB treatment. Only 13% of the untreated had complete records on the GxAlert database; some patients were not on treatment due to communication breakdown [27] * Mean diagnostic delay post consultation was 8.1 weeks for unknown reasons [28]		* Prolonged delay in receiving results from the lab caused some patients to drop out of care [2] * Difficulty in packaging, contamination, batching and transporting samples resulting in prolonged delays in diagnosis [25] *“We need to know how to package specimens in layers to avoid leakages and specimen rejections at the NRL” [25]* *“In a parcel of specimens, you could find one specimen 15 days old and another 3 days old…. I think they get a specimen, but they don’t send it on time. Instead they wait for them to be many before sending [25].* * Specimens received at late hours or not in sufficient numbers affect laboratory operations (9%+9%) [26]	* The use of the Expedited Mail Services for sample transportation helpful if sustained [25]
Clinic operational issues: Patient tracking and follow-up	* One reason for non-referral of patient to specialist care was failure to track patients (76%) [20] * Guidelines not implemented due to not having contact information for treatment facility (36%, 38%) in hospitals and clinics respectively [20]		* Failure or delay in tracking of patients to return for follow-up appointments and results not being available at follow-up appointments hampered access [2] *"In mid-August the ..clinic phoned me to check when I will be back home. They did not say why. I only went back at the .end of August and was informed...that I have MDR-TB. This was another shock for me. I was very disturbed that the clinic [had] not told me this while I was [away]. I was living unaware of this very contagious disease...I think this was very irresponsible of the clinic….”.* The delay in communicating results in this case was in fact 3 months [2]. * A lack of specimen referral mechanism noted as a challenge by almost of half of HCWs interviewed [26]	

Factor			Quantitative finding 95% CI [study ID] Barrier	Quantitative finding 95% CI [study ID] Facilitator	Qualitative finding [study ID] Barrier	Qualitative finding [study ID] Facilitator
	Service delivery					
		Clinic operational issues: Waiting times			* Long waiting times cited as a barrier [2] *"I don't like coming to the [public] clinic when I'm not feeling well…You wait for a long time before they can attend to you…At the [private] doctors room the treatment and waiting time was very reasonable. I only had to wait for 20 min. Here at the [public] clinic, you wait…you can wait for 8 hours here" [2].* * Long waiting times in the public sector pushed patients to seek care in the private sector, where options for TB care were not as many (Bieh et al., 2017b)	
		Level of care	* Patients referred from a hospital were eight times more likely not to initiate treatment than patients referred from a clinic [6]. * Patients accessing care in higher level facilities had slightly lower odds of getting tested compared with those in lower level facilities [22]	* The highest treatment initiation rate was among patients diagnosed through TB hospitals. Treatment initiation was lower among patients diagnosed in either secondary or tertiary hospitals compared to those diagnosed in primary health care facilities [4]. * Receiving care at a PHC facilitated access to treatment. Most adolescents started treatment at a primary health care facility compared to a district hospital or subacute facility [18] * Patients initiating as in-patients in a hospital were more likely to experience timely initiation of treatment than outpatients [21]. * Second specimen and monitoring testing rates were higher in clinics than in hospitals, while DST rates were higher in hospitals than in clinics for all 3 comparisons [15]		
		Public versus private sector care	* Patients in private sector had significantly lower odds of getting tested compared with those in public sector [22]		* Seeking care in the private sector noted as a barrier to testing (Bieh et al., 2017b) * Poor linkage to care between private and public sector [2], low index of suspicion at private facilities [28]. *"I went back again and again to the pharmacy and got different medication every time. I must have gone there five times" [2].*	* Public sector care identified as having more DR-TB care options [2] *"…. There are much better options at the [public] clinic than the private doctors…lots of test which can be taken…lots of tests which will find out what is wrong with you….For someone to get those things you have to be patient though" [2].*

Factor	Quantitative finding 95% CI [study ID]		Qualitative finding [study ID]	
	Barrier	Facilitator	Barrier	Facilitator
Service Delivery				
Location and coverage (rural/ urban)	* Less than half of RR-TB patients had DST results, with patients in the Western Cape twice as likely to have DST results than in the other provinces; this decreased by 3% every 30 days in Western Cape, suggesting difficulty in maintaining this standard [12] * DST testing rates and monitoring differed between provinces [15] * Geographic location of referral was not associated with treatment initiation time [16]. * Facilities that were >250 km away from NRL took longer from presumption of RR-TB to DST results compared to facilities <50km [23]. * Geographical differences noted in rates of samples collected for DST in HIV patients with presumptive DR-TB mostly for unspecified reasons [26] * Non-functional Xpert machines reported, varying by region (median of 2 months), reducing laboratory capacity for testing [26]	* Significant regional differences in treatment initiation rates and the TTI across the nine South African provinces in 2013: most showed significant increases in initiation rates, and all decreased TTI significantly [4]. * Western Cape patients were more likely to have second-line DST results than the remaining provinces, due to the specific provincial guidelines recommending the collection of 2 baseline samples [12] * Utilization of Xpert increased between 2016 and 2017 (88% increase). In 2017, utilization of Xpert was significantly higher in provincial than in district, then rural hospitals [13]. * Facilities that were <50km away from the NRL were more likely to have DSTs done compared to those >250 km away [23].	* Transportation of samples more difficult in rural areas [25] *“the transportation from Dar es Salaam Laboratory to the NRL is not a problem, they can use bodaboda or EMS. Actually, biggest problem is referring samples from peripheral laboratory to district laboratory where post services is not available” [25].*	Location and coverage (rural/ urban)
Health workforce				
Adherence to guidelines	* Despite complete rollout of Xpert testing, only 59% of new cases in the 2013 cohort were diagnosed initially with Xpert, with the rest diagnosed with LPA, and only 5% of these was due to non-availability of Xpert testing [4] * Less than half of RR-TB patients had DST results, as recommended by the South African National guidelines [12] * Patients screened incorrectly due to several reasons including mostly Xpert not conducted as outlined and cases of no follow up culture performed, nor specimen tested [17] * Guidelines not implemented due to patient follow-up perceived as difficult in all hospitals and clinics [20] * Poor adherence to guidelines resulting in under-utilization of Xpert, and counties with higher Xpert density not having significantly higher CNRs [22] * Incomplete adherence to National guidelines requiring DST for RR-TB patients, as DST was only done for 51% of patients [23]		* Health providers’ failure to follow diagnostic algorithms delayed DR-TB testing and led to wrong (first line) treatment regimens [2] *“When the results came back they told me I do not take my tablets. I told them ‘but I take my pills every day’. They could not understand why my results were 3-plus positive… In all the time that I took the treatment I felt the same. The treatment did not help....I started to give up hope” (Xpert-6- A high-risk DR-TB patient experienced 5-month delay due to not having a test done and initiation on first line treatment) [2]* .	Adherence to guidelines

Factor	Quantitative finding 95% CI [study ID] Barrier	Quantitative finding 95% CI [study ID] Facilitator	Qualitative finding [study ID] Barrier	Qualitative finding [study ID] Facilitator
Health workforce				
Workload and staff strength			* Laboratory staff shortages contributing to delays [1, 25] *“NRL staff have been trying to perform their work but they are overloaded with many specimens from each side of the country. One reference laboratory for culture and drug susceptibility testing... identify another branch to reduce congestions which causes results delays” [25].* * Shortage of trained laboratory staff to man the Xpert machines noted as a challenge by heads of laboratories [26]	
HCW knowledge, training, experience and supervision	* Poor adherence to Xpert algorithm especially in sending confirmatory tests, attributed to Xpert rollout preceding training of clinicians; only half of patients tested received confirmatory results [5]. * HCW knowledge, application and interpretation of molecular diagnostics below expected levels. Few were “able to describe well,” the technologies in use [26] * Frequency of untrained laboratory staff performing Xpert was common in all regions [26] * Only 41.7% of initial diagnoses were correct and a patient was started empirically on a DS-TB regimen without sending pleural fluid for TB culture, delaying DR-TB diagnosis 28]	* Most HCWs were more comfortable and knowledgeable using Xpert than other test types and it was the most common test used (72%) [26]	* HCW low index of suspicion for TB resulting in delayed diagnosis [2] *“I was at [the CHC] for 24 hours …they told me that I had infection in my lungs and gave me the drip and antibiotics…In the same month I didn’t feel so well so I went back… and they gave me the same drip and antibiotics”* [2]. *"I just feel some of the staff at the clinic is inexperienced." [29]* * Poor supervision leading to demotivation [25]	* Provider scheduling early return visits for DR-TB test results identified as a facilitator [2] * Support to the districts by the National program helpful if sustained [25] * *“there is a need to strengthen supervision, make it more fruitful not just a vehicle visiting. It needs to be supportive, get there, stay with the staff, for them to recognize and listen to their problems … then provide solution” [25]*
HCW motivation and attitude, including stigma and discrimination			* Assessment tests done outside the facility before treatment eg radiography/ audiometry were often not performed as other HCWs distanced themselves from DRTB services [1] * Fear of infection leading to HCW stigma and discrimination affecting both DR-TB HCWs and patients. Deliberate patients appointments cancellation noted [1] *"…some nurses and medical workers treated us like we are not fit to live.. They keep a distance when they want to communicate with us. If you come closer, they will shout go! go!! go!!! ... I felt like the worst person on earth having MDR-TB” [1]* * HCW blamed for lack of equipment and delays [1] * A lack of HCW motivation noted as a challenge to diagnosis and treatment [26]	* HCW attitude and counselling provided to patients expedited treatment acceptance and process [2] * Provider responsiveness at first contact and communicating concern about patients’ well-being facilitated early care [2] *"I … had mixed feelings [when I was told about MDR-TB]. …. At first, I did not understand this MDR-TB. I thought it was the end of time for me, but when the treatment process was explained to me, I felt much better and looked forward to the treatment" [2]*

Factor	Quantitative finding 95% CI [study ID] Barrier	Quantitative finding 95% CI [study ID] Facilitator	Qualitative finding [study ID] Barrier	Qualitative finding [study ID] Facilitator
Health information systems				
Data management	*Only 68% of specimens received by the laboratory had retrievable request forms [17] * Poor data capturing – 56% of patients with confirmatory samples were untraceable within 3 months of Xpert samples [5], 21% not found at all [21] * Data errors- missing data and 21.2% of treated patients not linked to diagnostic register likely indicative of missing patients [21] * Incomplete records likely contributed to why most patients (67%) of patients were untreated [27]		* Incorrectly filled laboratory requests forms leading to misplaced results [25] *"This is a long-standing problem laboratory request forms not filled in well, a lot of information is missing. We see forms coming with either one name or just initials and the rest of the information not filled in" [25].* * Unreliable patient addresses a challenge for HCWs [26]	
Access to second line diagnostics, medications and technologies				
Type of diagnostic test	* Median time to treatment reduced to 0 days for Xpert positive patients, compared to 14 days for empiric TB and suggestive chest x-ray findings, and 144 for culture positive, Xpert-negative patients [9] * Use of LPA was associated with delays in diagnosis and treatment, mostly due to prolonged laboratory TAT [19]	* LPA introduction associated with reduced TTI from 76 to 50 days). Xpert associated with a further reduction to 8 days in 2013 [3]. * Laboratory TAT reduced from 38 days in 2011 to 2 days in 2013 for new RR-TB cases; and in 2013 to 1d for patients diagnosed with Xpert, 29 days for LPA and 47d for phenotypic DST [4] * LPA diagnosis versus liquid culture reduced laboratory TAT from 52 days to 26 days, and TTI from 79 to 54 days; and from 89 days to 73.5 days for smear positives and negatives respectively [8] * Compared with culture, patients diagnosed with LPA were 73.3% less likely to be initiated late on treatment [10]. * Patients diagnosed with Xpert were more likely to have an earlier TTI when compared with DST culture, after adjusting for HIV status [11]; and were less likely to have late TTI (after 60 days[11]. * TTI in the Xpert-based algorithm was 17 days, with a median laboratory turnaround time of 1 day. There was a decrease of 25 days in median MDR-TB TTI in the Xpert-based algorithm [19].	* Older diagnostic tests prolonged diagnostic process [25] *"I would say the methods used to examine the specimens ... I think it is a big challenge because we need to be able to get these results quicker, for instance, they could be examined by liquid culture and drug susceptibility testing is done using molecular methods these could give results quicker" [25].*	
Access to second line diagnostics, medications and technologies				

Factor	Quantitative finding 95% CI [study ID]		Qualitative finding [study ID]	
	Barrier	Facilitator	Barrier	Facilitator
Access to second line diagnostics, medications and technologies				
Newer diagnostics impact on rates	* Treatment initiation rates remained unchanged with Xpert [3]. * Diagnosis with Xpert test did not significantly impact the treatment gap compared with other methods [4] * Treatment non-initiation rates did not differ significantly between the LPA (9%) and Xpert-based algorithm (6%) [19] * The total number of cases detected did not increase following the introduction of Xpert [24]	* The proportion of RR-TB cases diagnosed by Xpert increased from 43% to 61% with increased Xpert implementation. The proportion who initiated treatment increased from 43% to 60% also. [7]		
Access to testing products	* Unavailable diagnostic services in campus health facilities and students were referred to private or public hospitals [28].	* Full implementation of Xpert resulted in increased diagnosis rates (20%) and timeliness (92%), treatment referral and initiation (15%), increased treatment timeliness (49%), and decreased deaths before treatment (66.9%) [7]	* Stock outs of Xpert cartridges and reagents reported as a challenge by HCWs [26]	
Initial negative or invalid tests			* An initial negative test result delayed diagnostic process [2] *"So finally after three days the results came back.... they said I was negative, but I was still getting sicker... I went to [the CHC] again... I told the doctor 'I already gave sputum' and I went for x-rays and that's when she saw the x-ray and sent me straight here and they … put me on treatment" [2].*	
Health financing				
TB health financing			* Inadequate health financing resulted in a poor access to care or catastrophic costs for patients [28]. *Funding for sample transportation [28] *"… Who will take the specimens to the stations and who will pick the specimens up … and who will pay the costs for sending specimens? We had a partner, but their contract ended. So, that is still hanging in the air ..."* [28]	
Patient level (based on the Andersen and Newman Health Services Utilization model)				

Factor	Quantitative finding 95% Confidence Interval (CI) [study ID]		Qualitative finding [study ID]	
	Barrier	Facilitator	Barrier	Facilitator
Predisposing characteristics				
Sex	* Sex not associated with having a DST done [12, 23], nor with treatment initiation rates or timeliness [4,16, 19, 21] * Females less likely to have TB screening on hospital presentation with TB-related symptoms, OR=0.6 [14] * Laboratory turnaround time was increased for females was 1.09 times longer than for males [12]. * The mother being the TB source case resulted in children being more likely to miss clinic appointments OR= 3.78 [29]	* Being male was associated with increased odds of getting and Xpert test in all age groups [22]. * Females more likely to have timely diagnosis as males were 89.3% more likely to be diagnosed after 12 days compared with those diagnosed in 2 days or less, even when adjusted for the HIV status [10].		
Age	* Patients aged 55 and older had lower treatment initiation rates than patients aged 45–54 years [4] * TTI was longer for children aged 0–15 years compared to those aged 16–24 years [4] * Patients age ≤10 years were less likely to have a DST result[12] * Age was not associated with time to diagnosis [10], nor having a DST done [23], nor with rates of treatment initiation [18] or timeliness [19]. * Adults (ages 20–59) were less likely than children (0–19) to be initiated on treatment [21] * Less than 5% of patients 0-14yrs and 12.2% of patients ≥15yrs had an Xpert test done, resulting in reduced odds of getting an Xpert test in children, and in children mostly received chest X-rays, instead of microscopy testing [22]	* Adults aged 55 years and above were more likely to be screened for TB on hospital presentation for other reasons than those aged 18–24 years[14] * Middle-aged adults 35-44 years had higher case notification rates, whereas it was the lowest for children 5-9 years [22]		
Pregnancy			* Being pregnant made it more difficult to access TB care, resulting in transmission to family members [2] *"I was coughing and having sharp pains under my breast… I was feeling cold all the time, even shaking. They said they could not help me because I am pregnant...It was a very bad pregnancy, I even lost weight" [2]*	

Factor			Quantitative finding 95% CI [study ID]		Qualitative finding [study ID]	
			Barrier	Facilitator	Barrier	Facilitator
	Predisposing characteristics					
		Presenting symptoms and history	* Patients with smear-negative disease were less likely to have second-line DST results than patients with smear-positive disease 12]. * Differences in resistance patterns - Patients from the Western Cape had more INH resistance detected and additional forms of resistance than patients from the other provinces; leading to increased likelihood of ineffective DR-TB treatment [12]. * Patients with fever and patients with any two symptom combination (cough, fever, weight loss, night sweats) were less likely to be screened for TB on hospital presentation for other reasons, than those with symptom 3 or 4 symptom combinations [14]	* Patients with any 3 or 4 symptom combination (cough, fever, weight loss, night sweats) were more likely to be screened for TB on hospital presentation for other reasons [14] * Retreatment cases (i.e. failures, relapses/recurrences, defaulters) had the highest odds of getting an Xpert [22] * Being underweight, especially in children aged 0-14 years doubled the odds of receiving an Xpert test [22].	* Half the patients had previously been treated for TB but that did not always translate to symptom recognition or timely health seeking *"I did not believe it could be TB again because I completed my treatment the first time" [2].*	* Half the patients were previously treated for TB and several recognized the symptoms as a recurrence, responding by quickly seeking help at a PHC facility *"I had all the symptoms that I had the last time when I had TB. So I wanted them to check [for TB]"* [2].
		HIV status	* Treatment initiation rates among HIV-positive patients was lower than among HIV-negative patients and very low among patients with unknown HIV status; especially with Xpert diagnosis [4]. *HIV negative patients were less likely aOR=0.6 to start treatment compared to HIV positive [6] * HIV status was not associated with having a DST done [23], nor with treatment initiation time [11, 16]	* Odds of receiving TB diagnosis higher if HIV-positive using Xpert than for ART-naïve [9] * HIV+ patients had nearly twice the odds of receiving an Xpert test [22].	* Fear of an HIV diagnosis delayed care seeking [2] "My mother said I must go to the clinic for a TB test. She was worried that I may have TB because my [relative] also had TB. I did not want to go ...too scared that if I go for a TB test, they will also test me for HIV" [2]	* Some HIV-infected patient had an awareness of their increased risk of TB [2] *"I was coughing, my bones pained and I was losing weight...I thought I had TB ...I went to the ARV doctor because I had an appointment ... and told him how I feel. I asked him to send me for a TB test" [2]* *"I knew I was HIV positive, and that made me more worried when I felt sick. Even when my TB results were negative...I went again for a TB test" [2]*

Factor			Quantitative finding 95% CI [study ID] Barrier	Facilitator	Qualitative finding [study ID] Barrier	Facilitator
		Predisposing characteristics				
		Self-denial and non-disclosure			*Non-disclosure, stigma and discrimination in interacting with family and community likely delayed care [1] *“An illness that will make doctors and nurses to run away, if you tell a non-medic, will they stay with you? It’s just my family members. ... Not even to my friend. We do things together but I cannot tell them. Not even my girlfriend” [1]* * Fear of imprisonment and being exterminated in the hospital noted as a barrier [1] * Symptom minimization or denial, referring to these as “just a cough” or “just losing weight”, resulted in some patients presenting for care when they were extremely ill, having lost substantial weight or being too ill to walk [2]. *“But at all these times I was not sick. It was just a cough, sweat at night and I felt that I was also losing weight, nothing else, not a day I ever felt like I was sick” [2].*	
		Lifestyle and ethnicity	* Patients had a higher likelihood of missing clinic appointments when cigarettes were smoked in the house [29] * Colored patients when compared with Xhosa were less likely to attend clinic appointments for DR-TB care [29] * Colored more likely delayed diagnosis [29]			

		Patient agency, knowledge and perceptions	* Patients concerned about the risk of DR-TB infection at the clinic: OR= 2.45 (1.07–5.60, p=0.03); and those with perception of long waiting times not attending clinic OR=2.47 (1.07–5.69, p=0.03) [29]		* Failure to recognise TB symptoms and lack of awareness that TB can recur resulted in delayed care-seeking [2] *“I was having a terrible cough and I was sweating at night, but this did not ring an alarm for me, because I still thought this was just a fever and the change of season and that everything was going to be fine” [2]* * Negative perceptions of the public sector (over-burdened; long waiting times; negative staff attitudes; lack of privacy) [2] “*I was expecting long queues and sitting for ages before getting help. I am not sure what the situation is at the other clinics, but ... there was no queue and I got helped within 10 min...Staff in the TB room is very helpful and treats the patients with respect” [2]* * Beliefs of superstitions among patients prevented proper care [27]	* Earlier care-seeking was enabled by symptom recognition based on social contact with TB/MDR-TB patients or an awareness of increased risk of TB amongst HIV-infected patients [2] *“I did not know much about MDRTB. My [relative] had MDR-TB and told me to check if I don’t have it” [2]* * Perceptions of good quality service and familiarity with service [2] * Patient’s agency in specifically requesting TB screening services that were not offered facilitated early diagnosis [2] *“I knew I was HIV positive, and that made me more worried when I felt sick. Even when my TB results were negative...I went again for a TB test” [2].* * Patient agency and patience in waiting for care [2] *“I waited for a long time before I was attended, but I understand that is the way it is. There are lots of people that need to be attended to everyday here at the clinic. But I knew that at the end of the day I was going to get assisted. I just told myself that... I am sick already and I need help and in order for me to get help I must be patient” [2]*
	Enabling characteristics					
		Family, school or work support/ commitments	* Health seeking delay was 3.2 weeks (0 - 16 weeks, SD 4.6) due to fear of missing academic teaching and clinical duties [28]		* Family/work/school commitments or dissatisfaction with the service preventing a return to facilities or interruptions to the diagnostic process [2, 28, 29]. *“The day.. I was told I have MDR-TB, my family phoned… that my sister passed away. Everything then went crazy. All I could think about then was the fastest way to get [home.] I am the eldest son and must make all the preparation and decisions for the funeral. I left very early the next morning…not thinking about my MDR-TB treatment, maybe because my mind was very occupied with my family responsibilities …” [2].* ** ‘I got to campus health and asked, “I want to get my medication here,” and they told me, “No we don’t do that.” I asked where students get their medication and the sister said, “You have to go to a registered TB clinic”. I said, “Sister but I don’t have a car. When am I going to go? I have classes.” ... Then I went to occupational health and [the sister working there] said “I can’t do anything for you" [28]* *"The other reason is also that some parents found it very difficult to get time off from work" [29].*	Family support enabled early care-seeking [2]

Factor	Quantitative finding 95% CI [study ID] Barrier	Facilitator	Qualitative finding [study ID] Barrier	Facilitator
Enabling characteristics				
Loss to follow-up or death	* 31.2% of patients died before initiation but after diagnosis, 46.4% were lost to follow-up [6] * Main reason for patients' non-referral to specialist care was LFTU: 76% and 52% respectively for hospital and PHC diagnosed patients [20] * High mortality before referral was 19% of those diagnosed in hospital versus 33% of patients diagnosed in PHC [20]. * Only 32% new RR-TB cases notified were placed in an DR-TB regimen. 38% of those with complete records were untraceable and 26% died before treatment [27] * Of 6 patients who were not placed on treatment, 1 out-migrated and 1 died before treatment [18].		* Symptoms worsening and death before treatment [27] *'...this patient was a traditional healer, after a couple of days, his condition became worse; he decided to contact RTLC for help. RTLC made a quick logistical arrangement for a car from KIDH, but the patient died before taken to KIDH' [27].* * Patients reluctant to disclose proper addresses due to confidentiality concerns [28]	
Direct and indirect costs of care	* More than one minibus taxi required to get to DR-TB clinic was associated with children missing clinic appointments [29] * Substantial healthcare costs were incurred for DR-TB. Students struggled to obtain treatment and incurred high transport costs and missed academic time [28].		* Lack of transportation cost to keep appointments [2] * Participants reported substantial expenses, including specialist appointments, investigations, treatment costs [28]	
Geographic location	* Informal settlement: aOR=0.4 and suburb 0.3 and prison 0.1 less likely to start treatment compared with township residence [6] * Late DR-TB treatment Initiation (after 60 days) was less likely in patients having a town address (11] * Patients in 2 Eastern regions, SE and NE, less likely to be treated than the SW, with variable patterns within states in the same region; and patients in semi-urban 2 times more likely to initiate treatment early than those in urban locations [21]	* City/town residence was more likely to initiate treatment compared with township residence [6] * Patients living in semi-urban areas were more likely to experience timely initiation of treatment than those in urban areas [21].		* Convenience of free, accessible local services enabled early care-seeking [2]
Need characteristics				
Treatment refusal	* Of 6 patients who were not placed on treatment, 4 were due to patient factors- including 2 treatment refusals [18].			
Health seeking practice				
Alternative care	* Patients opt for traditional medicine and do not return for results [26]		* Cultural beliefs and seeking traditional healthcare (often in another province) [2] * Patients opting for traditional medicine and not returning for results noted as a challenge to care by HCWs [26]	

Abbreviations: IDI- In-depth interviews; FGDs - Focus group discussions; KIIs- Key informant interviews; HCW- Healthcare worker; HS= health system; TTI-Time to treatment initiation; SL- Second line; NRL- National or Central TB Reference Laboratory;; TB- Tuberculosis; RR-TB- Rif-resistant TB; DR-TB- Drug resistant TB; Xpert- GeneXpert MTB/RIF Assay; LPA- Line Probe Assay; DST- culture/phenotypic drug sensitivity testing; RR-Risk Ratio. LTFU- Lost to follow-up

Notes on studies:

#1 - Even though a study of patients already on treatment, some issues like discrimination have been shown in other studies to impact patient access to care

#28 - Distinguishing between factors related to diagnosis/treatment access from impact of treatment

Provider knowledge, skills and attitude (KSA) were repeatedly shown to influence access and was a predominant theme (*Fig 3*). Delayed or inadequate training, inexperience and poor supervision of health workers influenced product availability, diagnosis and treatment (Doulla et al., 2019, Mpagama et al., 2013, Zimri et al., 2012, van der Westhuizen and Dramowski, 2017, Dlamini-Mvelase et al., 2014, Naidoo et al., 2015a). Poor adherence to DR-TB testing algorithm, treatment guidelines or referral procedures hampered diagnosis and treatment (Nkosi et al., 2013, Cox et al., 2017, Jacobson et al., 2017, Mohr et al., 2017, Oliwa et al., 2018, Timire et al., 2019, Naidoo et al., 2015a), with patients often left undiagnosed, untreated, treated with ineffective drugs or only after serious complications (Nkosi et al., 2013, Naidoo et al., 2015a).

At the patient level, poor perception of the public sector (over-burdened, long waiting times, negative staff attitudes, poor confidentiality, lack of privacy, risk of infection) were some reasons why patients were avoiding the public sector hospitals where DR-TB services could be accessed (Naidoo et al., 2014b, Zimri et al., 2012, van der Westhuizen and Dramowski, 2017, Bieh et al., 2017b).

Wrong disease attribution, symptom minimization, non-disclosure, treatment refusal and choosing traditional care to were also noted as delaying care-seeking (Bieh et al., 2017b, Moyo et al., 2014, Mpagama et al., 2013, Naidoo et al., 2015a).

Patients seeking care first in the private sector care (private hospitals, pharmacies, patent medicine vendors, traditional healers), where the index of suspicion was lower, instead of public sector, where services were available, had lower odds of getting tested (Oliwa et al., 2018).

Acceptability/ability to seek

Our review found that although provider attitudes and practice were implicated, patients' predisposing characteristics were predominant in influencing their decisions to utilize health service (Levesque et al., 2013, Andersen and Newman, 2005, WHO, 2007). Acceptability challenges were related to poor healthcare worker norms and attitude including confidentiality concerns, stigma and how the care patients received were influenced by their symptoms (Cox et al., 2015, Cox et al., 2017, Kweza et al., 2018, Oliwa et al., 2018) or sociodemographic characteristics (Bieh et al., 2017b, Zimri et al., 2012). Patient's ability to seek were influenced by their sociodemographic characteristics, personal, cultural and social values, disclosure, work and family commitments, use of private sector alternatives, and fear of poor infection control (Zimri et al., 2012, Moyo et al., 2014, Mnyambwa et al., 2018, Timire et al., 2019, van der Westhuizen and Dramowski, 2017, Oga-Omenka et al., 2019, Oliwa et al., 2018, Naidoo et al., 2014b, Jacobson et al., 2017, Hanrahan et al., 2012, Ebonwu et al., 2013, Naidoo et al., 2015a).

At the provider level, stigma and discrimination towards providers from other hospital workers, and from provider to patients compromised access to and quality of care (Bieh et al., 2017b, Mpagama et al., 2013, Naidoo et al., 2015a).

At the patient level, living with HIV had conflicting results. Some studies found no association between HIV status and having a DST done, nor with time to treatment (Metcalfe et al., 2016, Iruedo et al., 2017). However, two studies found HIV patients having overall higher odds of receiving a TB diagnosis (Hanrahan et al., 2013, Oliwa et al., 2018). However, HIV positive patients had longer times to treatment or were less likely to initiate treatment (Cox et al., 2015, Cox et al., 2017), except in one study where treatment initiation rates were higher than in HIV negative patients (Ebonwu et al., 2013). In qualitative studies, the fear of an HIV diagnosis delayed health-seeking, and some HIV patients were seen to have an increased awareness of TB risk (Naidoo et al., 2015a).

Patients presenting with more than two symptoms combination (cough, fever, weight loss, night sweats), retreatment cases and undernourished children were more likely to be screened for TB on hospital presentation for other reasons than those presenting with fewer symptoms, new cases, and well-nourished children respectively (Kweza et al., 2018, Oliwa et al., 2018). Smear-positive cases and more symptomatic patients were more likely to have a DST done (Jacobson et al., 2017, McLaren et al., 2017). Half of the time, previous TB led to faster symptom recognition and care seeking (Naidoo et al., 2015a). In one study, being pregnant made accessing DR-TB care more difficult as providers refused to initiate any DR-TB related care (Naidoo et al., 2015a).

Patient agency and persistence in demanding DR-TB testing where none was offered was noted as a facilitator to DR-TB healthcare, and this was linked to HIV positivity or prior knowledge of the disease, either through an earlier TB disease or knowing another DR-TB patient (Naidoo et al., 2015a).

Results linking access to patient gender and age were largely inconclusive. In several studies, neither patient gender nor age were found to be associated with diagnosis timeliness or rates (Jacobson et al., 2017, Timire et al., 2019, Iruedo et al., 2017), nor with treatment initiation rates or timeliness (Cox et al., 2017, Metcalfe et al., 2016, Naidoo et al., 2014b, Moyo et al., 2014). There were some indications that females (Kweza et al., 2018, Oliwa et al., 2018) or children whose mothers are the primary TB source (Zimri et al., 2012), or younger age (Kweza et al., 2018, Oliwa et al., 2018, Cox et al., 2017, Jacobson et al., 2017) were less like to be diagnosed or treated. (Table 2). One study (Oga-Omenka et al., 2019) found children to be more likely to initiate treatment than adults.

One study noted other contextual patient factors that were seen to influence DR-TB care. In South Africa, *ethnicity* and *cigarette smoking* - with children failing to attend clinic appointments more frequently from colored ethnicity and homes with cigarette smokers. No particular reason was given for these differences, however, it was acknowledged that these were markers for other socioeconomic and cultural factors needing further research (Zimri et al., 2012).

Availability/ability to reach

These were mostly related to service delivery, access to health products and patient tracking on the provider side, and geographic access and life commitments on the patient side (Levesque et al., 2013, Andersen and Newman, 2005, WHO, 2007). Specific health system barriers were related to coverage, bed spaces and centralization of services; inadequate availability and coverage of health products- equipment and technology, advanced diagnostics and medications; shortages of health personnel; clinic and laboratory errors (Bieh et al., 2017b, Van Den Handel et al., 2015, Zimri et al., 2012, Cox et al., 2015, Iruedo et al., 2017, Jacobson et al., 2012, Mohr et al., 2017, Hanrahan et al., 2012, Mpagama et al., 2013, McLaren et al., 2017, Jacobson et al., 2017, Naidoo et al., 2014b, Timire et al., 2019, Mnyambwa et al., 2018, Doulla et al., 2019, Oga-Omenka et al., 2019, Evans et al., 2018, Hanrahan et al., 2013, Jokwiro et al., 2018, Naidoo et al., 2015a). Patients were prevented from reaching health services when they lived in inaccessible locations or faraway distances, lack of social support, and difficulty in transportation, poor sputum specimen, out-migration or death (Bieh et al., 2017b, Van Den Handel et al., 2015, Zimri et al., 2012, Jacobson et al., 2017, Jokwiro et al., 2018, Oga-Omenka et al., 2019, Moyo et al., 2014, Nkosi et al., 2013, Ebonwu et al., 2013, Hanrahan et al., 2012, Naidoo et al., 2015a).

Laboratory operational challenges were the most reoccurring barriers to care (*Fig 3*). Specimen contamination, loss of viability, difficulty in packaging, batching, transportation and delivery of samples (Jacobson et al., 2017, Mpagama et al., 2013, Doulla et al., 2019) delayed diagnosis. Not requesting tests, incomplete records, delayed results were other barriers preventing patients form accessing care (Mpagama et al., 2013, van der Westhuizen and Dramowski, 2017, Timire et al., 2019, Doulla et al., 2019, Mnyambwa et al., 2018, Naidoo et al., 2015a). Staff shortages, especially laboratory staff, contributed to diagnostic delays and patient waiting times (Bieh et al., 2017b, Doulla et al., 2019, Mpagama et al., 2013). There were significant geographical variations, mostly in laboratory operations, which impacted referral, diagnosis and treatment rates (Oga-Omenka et al., 2019, Jacobson et al., 2017, McLaren et al., 2017, Metcalfe et al., 2016, Timire et al., 2019, Mpagama et al., 2013, Jokwiro et al., 2018, Doulla et al., 2019, Cox et al., 2017). National program support to health centers and using expedited mail service for sample transportation were helpful in reducing laboratory delays (Doulla et al., 2019).

Poor data management affected patient linkage to care and reporting. Errors including missing patient records in diagnosis or treatment registers, irretrievable request forms, incomplete data entry led to misplaced results, untraceable patients and poor linkage to care (Doulla et al., 2019, Mpagama et al., 2013, Oga-Omenka et al., 2019, Mohr et al., 2017, Mnyambwa et al., 2018).

Inadequate coverage and maintenance of diagnostic equipment, as well as power outages hampered diagnostic capacity (Bieh et al., 2017b, Doulla et al., 2019, Mpagama et al., 2013, Oliwa et al., 2018) and staff motivation (Bieh et al., 2017b). Where available, using the Xpert notification system improved team communication and facilitated diagnosis (Mnyambwa et al., 2018).

Centralization (in few specialized health centers) of GeneXpert MTB/RIF (Xpert) or other pre-treatment requirements like x-rays, and a lack of integration, increased diagnosis time (Naidoo et al., 2014b, Doulla et al., 2019), and resulted in negative patient experiences (Bieh et al., 2017b). Service decentralization (wider spread availability of services, and at the different healthcare levels) was, consequently shown to be a major facilitator of access (*Fig 3*), reducing time to diagnosis and treatment, and increasing diagnosis rates (Cox et al., 2015, Evans et al., 2018, Moyo et al., 2014, Timire et al., 2019, Van Den Handel et al., 2015, Hanrahan et al., 2013, Naidoo et al., 2015a). However, patients initiating care at higher facilities had lower odds of getting tested or initiating treatment (Ebonwu et al., 2013, Oliwa et al., 2018, Moyo et al., 2014). Treatment initiation rate was highest among patients diagnosed directly through TB hospitals (Cox et al., 2017). In one setting, timeliness of treatment was higher among patients initiated as in-patients compared to outpatients (Oga-Omenka et al., 2019).

The public sector had longer waiting times pushing patients to access care in the private sector, with poor linkages between the two (van der Westhuizen and Dramowski, 2017, Naidoo et al., 2015a). Failure or delay in tracking patients, and unavailability of results at appointments prevented access (Mpagama et al., 2013, Naidoo et al., 2015a).

Access to newer diagnostics was the principal facilitator of access identified (*Fig 3*). There was an overall consensus that the use of older diagnostic tests (e.g. x-rays, drug susceptibility testing (DST) or line probe assay (LPA), when compared with Xpert, was associated with longer times to diagnosis and treatment (Jacobson et al., 2012, Cox et al., 2017, Iruedo et al., 2017, Van Den Handel et al., 2015, Naidoo et al., 2014b, Dlamini-Mvelase et al., 2014, Hanrahan et al., 2013, Cox et al., 2015, Hanrahan et al., 2012, Doulla et al., 2019). With the exception of one study (Evans et al., 2018), Xpert implementation did not result in corresponding increases in diagnosis and treatment rates (Van Den Handel et al., 2015, Cox et al., 2015, Cox et al., 2017, Naidoo et al., 2014b). Also, the average time to DR-TB care remained significantly higher than the national targets in most settings (Cox et al., 2017, Iruedo et al., 2017, Naidoo et al., 2014b, Dlamini-Mvelase et al., 2014, Jacobson et al., 2012, Oga-Omenka et al., 2019).

At the patient level, several studies noted high rates of patients being lost to follow-up or dying before treatment due to non-referrals, data errors, prolonged pre-treatment processes and delayed care-seeking (Ebonwu et al., 2013, Nkosi et al., 2013, Mnyambwa et al., 2018).

Geographical location of patients was also identified as an access barrier. Patients in an urban/formal settlement accessed care more compared to those in rural, informal settlements or prison. Other variations were likely linked to the healthcare location, as noted above (Ebonwu et al., 2013, Jacobson et al., 2012, Oga-Omenka et al., 2019, Naidoo et al., 2015a). Significant variations in accessing diagnosis and treatment were due to geographical locations of the patients, with urban residence or proximity to care facility increasing likelihood of testing and treatment, as well as reducing time to results and treatment (Jacobson et al., 2017, McLaren et al., 2017, Metcalfe et al., 2016, Timire et al., 2019, Mpagama et al., 2013, Cox et al., 2017, Jokwiro et al., 2018, Doulla et al., 2019).

Family, work or school commitments were seen to prevent or interrupt the care process, while the presence of family support enabled care-seeking (Zimri et al., 2012, van der Westhuizen and Dramowski, 2017, Naidoo et al., 2015a).

Affordability/ability to pay

The financial implications of services were mostly related to the enabling characteristics of patients to pay for care including transportation costs Levesque et al. (2013), (Andersen and Newman, 2005, WHO, 2007). In our review, we found difficulties in paying for transport to health facilities, and high opportunity costs borne by patients (Zimri et al., 2012, Naidoo et al., 2015a).

Ease of accessibility and cost of health services were some reasons for choice of facility. A lack of money for transport, travel time and numerous bus transfers influenced whether they returned to facility after initial visit (Naidoo et al., 2014b, Zimri et al., 2012, van der Westhuizen and Dramowski, 2017). Seeking care in the private sector was noted as contributing to the high costs of care for patients, as some go the public sector, where care was perceived as poor, only when they could no longer afford private care (Naidoo et al., 2015a). In another study where high costs of care was noted, majority of the patients sought care in the private sector (van der Westhuizen and Dramowski, 2017).

Table 3: Paired Access Dimensions and Recommendations

Structural Access Dimensions and Barriers (Study ID #)	**Patients Access Dimensions and Barriers (Study ID #)**	**Recommendations (Study ID #)**
Approachability: - Outreach - Lack of patient tracking and follow up (6, 7, 20) - Referrals from clinics or private facilities to DRTB care centers not done (4, 6, 20) - Poor HCW information or knowledge of TB, resistance, guidelines or algorithms (2, 5, 7, 14, 26, 27, 29) - Lack of guideline knowledge and adherence (17, 20, 25, 27)	Ability to Perceive: - Poor knowledge of disease and perceptions of service (2, 27, 29) - Distrust and unmet expectations (2, 27)	- Raise public awareness of symptoms and the need for early care (2, 29) - Improve HCW knowledge/training and supervision on TB surveillance, resistance monitoring, guidelines and algorithms (2, 5, 11, 12, 14, 15, 20, 22, 27, 28) - Improve surveillance, data management, referral, and screening e.g. intensified case finding, appointment of dedicated linkage officers in each district (2, 4, 5, 6, 7, 8, 17, 19, 14, 15, 22, 23, 25) - Increase access to newer, rapid diagnostics- point-of-care Xpert and ensure proper deployment and use (3, 5, 8, 9, 10, 11, 13, 18, 22, 26) - Use of home visits or alert systems to follow-up patients (5, 7, 20, 29) - Broad based policies and strategies to improve screening (5, 8, 15)
Acceptability: - Professional values, norms and attitude (1) - Care attributes- infection control, long duration of hospitalization/treatment (1, 29)	Ability to seek: - Personal and social values (2, 18) - Disclosure and confidentiality (1, 27) - Culture and gender norms (2) - Work and family commitments (2) - Patient sociodemographic characteristic, treatment history and co-morbidities (4, 6, 8, 12, 19, 21, 22, 23) - Choosing alternative care (2) - Fear of infection, delays or side effects (2, 28, 29)	- Improve service delivery including integration and retention in care- e.g. appointment of linkage officers in each district (2, 4, 6, 20) - Reduce hospitalization duration (1) - - Strengthen infection control measures and occupational health services (1, 27, 28, 29) - Increase home-based care of DR-TB (1, 20) - Improve visitation policies for hospitalized patients (1) - More attention to patient level barriers (21, 28)

Structural Access Dimensions and Barriers (Study ID #)	**Patients Access Dimensions and Barriers (Study ID #)**	**Recommendations (Study ID #)**
<u>Availability:</u> - Coverage/centralization of services (3, 24) - Bed spaces for hospitalization phase (8) - Health products- Inadequate supplies of diagnostics and drugs (26) - Personnel- shortages in HCW quantity and quality (1, 15) - Laboratory and clinic operational errors and delays (8, 11, 12, 15, 17, 19, 24, 25, 27) - Inadequate access to or low utilization of newer diagnostic instruments (2, 3, 7, 9, 10, 11, 13, 19, 26) - Regional operational differences (12, 21)	<u>Ability to reach:</u> - Poor sputum specimen (12) - Difficult transportation to facility (2, 13, 24, 29) - Lack of social support (1) - Geographic located far from care (6, 8, 12, 21, 24, 29) - Out-migration or death (18, 20)	- Decentralizing, linking and integrating services (3, 5, 8, 21, 24, 29) - Improve social and psychosocial support (1) - Increase HCW quantity and quality (15) - Enable same day treatment initiation after Xpert (24) - 2 sputum specimen at baseline (12) - Increase capacity and quality of in-patient and community-based care (8) - Ensuring continuous supply of health products (13) - Expanded and timely access to treatment regimens, facilities and strategies (8, 21, 23)
<u>Affordability:</u> - Program structure (2, 28, 29) - Lack of funding for sputum transportation and consumables (25)	<u>Ability to pay:</u> - Inability to pay for transport or treatment requirements; opportunity costs (29)	- Increased government investment (25)

Discussion

Our review synthesizes the diverse knowledge base about obstacles to DR-TB care in SSA to create a consolidated understanding to inform practice. It highlighted several health system and patient barriers.

Our key findings include the role rapid diagnostics and laboratory operational issues play in facilitating or impeding access. Rapid diagnostic tools, particularly Xpert, play a central role in accessing DR-TB diagnosis and treatment, and their absence would constitute a significant barrier to receiving care (Doulla et al., 2019, Hanrahan et al., 2013, Naidoo et al., 2014b). The introduction of these tools has led to a significant reduction in times to care for DR-TB (Cox et al., 2015, Cox et al., 2017, Hanrahan et al., 2012, Hanrahan et al., 2013, Iruedo et al., 2017, Jacobson et al., 2012, Naidoo et al., 2014b). However, although times were shortened, patients still experienced unnecessary delays in accessing care. The gains of rapid diagnostic technology have, so far, not translated into a commensurate increase in rates of detection and treatment (Naidoo et al., 2014b, Van Den Handel et al., 2015, Cox et al., 2017, Cox et al., 2015). These were likely due to the range of laboratory operational errors identified (Jacobson et al., 2017, Mpagama et al., 2013, Doulla et al., 2019, van der Westhuizen and Dramowski, 2017, Timire et al., 2019, Mnyambwa et al., 2018, Naidoo et al., 2015a), and which need to be targeted to improve case finding and treatment rates.

Our review data reveal several missed opportunities for screening and treatment initiation (Cox et al., 2015, Mohr et al., 2017, Kweza et al., 2018, Naidoo et al., 2015a). These contribute to the global ‘missing cases’, perpetuate transmission and highlight critical gaps in the care cascade. For example, the inadequate linkage between the private and the public sector occur before access to testing and are beyond the scope of rapid diagnostics. They contribute to the persistence of low diagnostic and treatment rates despite Xpert implementation.

Results for age and sex were found to be divergent, as many studies found both factors not significant in impacting care. In the studies where age was significant, younger age was mostly a barrier (Kweza et al., 2018, Oliwa et al., 2018, Cox et al., 2017, Jacobson et al., 2017), except in one study (Oga-Omenka et al., 2019) where the program prioritized children and other high-risk groups for Xpert diagnosis and in-patient care. Where most studies found sex not associated with DR-TB care, some found being female or a child or a female DR-TB patient to be a barrier to care (Jacobson et al., 2017, Kweza et al., 2018, Zimri et al., 2012, Oliwa et al., 2018). One study found females more likely to have earlier diagnosis, likely due to care-seeking behaviors (Iruedo et al., 2017).

Several contextual factors like language, religion and culture were not identified by the studies included in this review. Geographic locations of the health centers and of the patients themselves were identified as influencing access to care, and this has been reported by other authors (Sullivan et al., 2017, van de Water et al., 2017). Ethnicity and lifestyle were identified in one study to influence access, likely due to socio-economic and cultural implications (Zimri et al., 2012). The lack of qualitative data on the influence of sex and age on access makes it difficult to draw conclusions about whether the effects seen were due to contextual factors.

To improve patient-level barriers calls for a close examination of social determinants like poverty and geographic access as an addition to biomedical approaches, as recommended by the Commission on Social Determinants of Health (CSDH) (Hargreaves et al., 2011, Rasanathan et al., 2011, CSDH, 2008). The burdens of infectious diseases like TB are disproportionately borne by patients with certain socio-demographic characteristics. For example, rural patients bear higher treatment costs and report more difficulty with transport to health centers for treatment (Farmer, 1996, Bhutta et al., 2014a). Demographic characteristics such as gender, poverty or ethnicity often interact in complex ways, further increasing vulnerability and disadvantage (Marmot et al., 2012, Zarowsky et al., 2013). Inadequate knowledge of DR-TB disease and health services was also identified as a major cause of poor health-seeking behavior among patients. Raising public awareness of symptoms and available resources may contribute to reducing these delays.

The biomedical approach, which focuses more on the use of technology to manage diseases needs to be combined with efforts to tackle root causes and social determinants of DR-TB disease (Farmer, 1996, WHO, 2014c).

Our findings indicate that, in order to overcome prevailing barriers to care, innovative diagnostic tools and treatment require functional, efficient and accessible health systems to reach and track patients who are, themselves, informed and motivated. The high susceptibility of individuals of getting harmed from DR-TB, due to the complex interaction between risk factors and available resources, is manifest in their inability to manage risks or recover from the disease effectively (Zarowsky et al., 2013). This is corroborated by many of the reviewed studies in which diagnosed patients died before they could be initiated on life-saving treatment (Ebonwu et al., 2013, Moyo et al., 2014, Nkosi et al., 2013, Mnyambwa et al., 2018). This highlights the fact that DR-TB continues to be characterized by avoidable morbidity and deaths, especially in SSA, and must be treated with urgency. The *raison d'être* of rapid diagnostic methods is to improve these outcomes by facilitating quicker diagnosis and treatment. Xpert implementation did not translate to universal increases in diagnosis and treatment rates, presenting a significant setback and missed opportunity in the control of DR-TB.

Gaps in the capacity of the health system to deliver care need to be closed. This would require significant investments at lower levels of care towards more decentralized and ambulatory models of care. In order to fund these efforts, SSA governments need to prioritize and increase health investments and mobilize resources to fund TB control.

Strengths and limitations

The strengths of this review include the adaptation of our conceptual framework to align factors influencing DR-TB care with other well-known frameworks in the field of healthcare access and systems strengthening (Levesque et al., 2013, Andersen and Newman, 2005, WHO, 2007), using a mixed-methods approach.

This review has a few limitations. First, due to the heterogeneity of study methods and outcome variables, no summary measures (e.g. effect size) nor pooled analysis for specific interventions were determined, as the studies were not sufficiently comparable to each other. Another limitation is related to the location of the studies. Our search showed a dominance of studies from South Africa, with only two from Nigeria, and none from Angola, DR Congo, Ethiopia, Kenya, Mozambique, the other TB/DR-TB/HIV HBCs in the region. This may have affected the generalizability of our findings within the region, as there are likely other barriers in the different other settings that were not identified. However, the relatively higher HIV burden in South Africa, and the country's quick adoption of newer diagnostics and medications could serve as an example for these other countries as they scale-up services for drug resistant tuberculosis.

Conclusions

The implications of these findings are sobering; they suggest that despite significant progress in cutting down time to diagnosis and treatment by using rapid diagnostics, this is not enough, in itself, to remove all delays to diagnosis, as other barriers persist in the health system.

The WHO recognises that DR-TB is a social justice problem and as a threat to global health security, requiring universal access to the tools and services needed for rapid diagnosis, treatment and care (Organization, 2015). Diagnosis and treatment for DR-TB is a complex and multi-faceted socio-economic problem that needs to be addressed using a multi-sectoral approach (World Health Organization, 2014). Provider and patient level barriers need to be addressed to maximize the impact of advanced diagnostics. Most of the operational problems identified, such as the poor provider knowledge and implementation of DR-TB guidelines or inefficient screening or laboratory processes, are rectifiable, albeit with a substantial amount of effort and investment. We have identified this review as a call to action for all relevant players.

There is a need for more studies focusing on contextual access dimensions and care cascades from more HBCs in SSA, as this review has highlighted a dominance of studies from South Africa.

References:

ABEGAZ, T. M., SHEHAB, A., GEBREYOHANNES, E. A., BHAGAVATHULA, A. S. & ELNOUR, A. A. 2017. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. *Medicine,* 96.

ANDERSEN, R. & NEWMAN, J. F. 2005. Societal and individual determinants of medical care utilization in the United States. *The Milbank Quarterly,* 83**,** Online-only-Online-only.

BAILIE, J., SCHIERHOUT, G., LAYCOCK, A., KELAHER, M., PERCIVAL, N., O'DONOGHUE, L., MCNEAIR, T. & BAILIE, R. 2015. Determinants of access to chronic illness care: a mixed-methods evaluation of a national multifaceted chronic disease package for Indigenous Australians. *BMJ open,* 5**,** e008103.

BHUTTA, Z. A., SALAM, R. A., DAS, J. K. & LASSI, Z. S. 2014. Tackling the existing burden of infectious diseases in the developing world: existing gaps and the way forward. *Infectious diseases of poverty,* 3**,** 1.

BIEH, K. L., WEIGEL, R. & SMITH, H. 2017. Hospitalized care for MDR-TB in Port Harcourt, Nigeria: A qualitative study. *BMC Infectious Diseases,* 17 (1)

BOYD, R., FORD, N., PADGEN, P. & COX, H. 2017. Time to treatment for rifampicin-resistant tuberculosis: systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease,* 21**,** 1173-1180.

CLIFFORD, B. K., MIZRAHI, D., SANDLER, C. X., BARRY, B. K., SIMAR, D., WAKEFIELD, C. E. & GOLDSTEIN, D. 2018. Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review. *Supportive Care in Cancer,* 26**,** 685-700.

COX, H., DICKSON-HALL, L., NDJEKA, N., VAN’T HOOG, A., GRANT, A., COBELENS, F., STEVENS, W., NICOL, M. & VAN'T HOOG, A. 2017. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study. *PLoS Medicine,* 14**,** 1-19.

COX, H. S., DANIELS, J. F., MULLER, O., NICOL, M. P., COX, V., VAN CUTSEM, G., MOYO, S., DE AZEVEDO, V. & HUGHES, J. 2015. Impact of Decentralized Care and the Xpert MTB/RIF Test on Rifampicin-Resistant Tuberculosis Treatment Initiation in Khayelitsha, South Africa. *Open Forum Infectious Diseases,* 2.

CSDH 2008. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva: World Health Organization.

DHARMADHIKARI, A. S., MPHAHLELE, M., VENTER, K., STOLTZ, A., MATHEBULA, R., MASOTLA, T., VAN DER WALT, M., PAGANO, M., JENSEN, P. & NARDELL, E. 2014. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease,* 18**,** 1019-1025.

DLAMINI-MVELASE, N. R., WERNER, L., PHILI, R., CELE, L. P. & MLISANA, K. P. 2014. Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. *BMC Infectious Diseases,* 14.

DOULLA, B. E., SQUIRE, S. B., MACPHERSON, E., NGADAYA, E. S., MUTAYOBA, B. K. & LANGLEY, I. 2019. Routine surveillance for the identification of drug resistant Tuberculosis in Tanzania: A cross-sectional study of stakeholders’ perceptions. *PloS one,* 14**,** e0212421.

EBONWU, J. I., TINT, K. S. & IHEKWEAZU, C. 2013. Low treatment initiation rates among multidrug-resistant tuberculosis patients in Gauteng, South Africa, 2011. *International Journal of Tuberculosis and Lung Disease,* 17**,** 1043-1048.

EVANS, D., SINEKE, T., SCHNIPPEL, K., BERHANU, R., GOVATHSON, C., BLACK, A., LONG, L. & ROSEN, S. 2018. Impact of Xpert MTB/RIF and decentralized care on linkage to care and drug-resistant tuberculosis treatment outcomes in Johannesburg, South Africa. *BMC health services research,* 18**,** 973.

FARMER, P. 1996. Social inequalities and emerging infectious diseases. *Emerging infectious diseases,* 2**,** 259.

GANDHI, N. R., NUNN, P., DHEDA, K., SCHAAF, H. S., ZIGNOL, M., VAN SOOLINGEN, D., JENSEN, P. & BAYONA, J. 2010. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet,* 375**,** 1830-1843.

HANRAHAN, C. F., DORMAN, S. E., ERASMUS, L., KOORNHOF, H., COETZEE, G. & GOLUB, J. E. 2012. The impact of expanded testing for multidrug resistant tuberculosis using geontype MTBDRplus in South Africa: an observational cohort study. *PloS one,* 7**,** e49898.

HANRAHAN, C. F., SELIBAS, K., DEERY, C. B., DANSEY, H., CLOUSE, K., BASSETT, J., SCOTT, L., STEVENS, W., SANNE, I. & VAN RIE, A. 2013. Time to Treatment and Patient Outcomes among TB Suspects Screened by a Single Point-of-Care Xpert MTB/RIF at a Primary Care Clinic in Johannesburg, South Africa. *Plos One,* 8.

HARGREAVES, J. R., BOCCIA, D., EVANS, C. A., ADATO, M., PETTICREW, M. & PORTER, J. D. 2011. The social determinants of tuberculosis: from evidence to action. *American journal of public health,* 101**,** 654-662.

HELLER, T., LESSELLS, R. J., WALLRAUCH, C. G., BARNIGHAUSEN, T., COOKE, G. S., MHLONGO, L., MASTER, I. & NEWELL, M. L. 2010. Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. *International Journal of Tuberculosis & Lung Disease,* 14**,** 420-6.

HONG, Q. N., FABREGUES, S., BARTLETT, G., BOARDMAN, F., CARGO, M., DAGENAIS, P., GAGNON, M.-P., GRIFFITHS, F., NICOLAU, B. & O'CATHAIN, A. 2018. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Education for Information***,** 1-7.

IRUEDO, J., O'MAHONY, D., MABUNDA, S., WRIGHT, G. & CAWE, B. 2017. The effect of the Xpert MTB/RIF test on the time to MDR-TB treatment initiation in a rural setting: a cohort study in South Africa's Eastern Cape Province. *BMC Infectious Diseases,* 17**,** 1-9.

JACOBSON, K. R., BARNARD, M., KLEINMAN, M. B., STREICHER, E. M., RAGAN, E. J., WHITE, L. F., SHAPIRA, O., DOLBY, T., SIMPSON, J. & SCOTT, L. 2017. Implications of failure to routinely diagnose resistance to second-line drugs in patients with rifampicin-resistant tuberculosis on Xpert MTB/RIF: a multisite observational study. *Clinical Infectious Diseases,* 64**,** 1502-1508.

JACOBSON, K. R., THERON, D., KENDALL, E. A., FRANKE, M. F., BARNARD, M., VAN HELDEN, P. D., VICTOR, T. C., STREICHER, E. M., MURRAY, M. B. & WARREN, R. M. 2012. Implementation of GenoType MTBDR plus Reduces Time to Multidrug-Resistant Tuberculosis Therapy Initiation in South Africa. *Clinical infectious diseases,* 56**,** 503-508.

JOKWIRO, A., TIMIRE, C., HARRIES, A., GWINJI, P., MULEMA, A., TAKARINDA, K., MAFAUNE, P. & SANDY, C. 2018. Has the utilisation of Xpert® MTB/RIF in Manicaland Province, Zimbabwe, improved with new guidance on whom to test? *Public health action,* 8**,** 124-129.

KWEZA, P. F., VAN SCHALKWYK, C., ABRAHAM, N., UYS, M., CLAASSENS, M. M. & MEDINA-MARINO, A. 2018. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. *International Journal of Tuberculosis and Lung Disease,* 22**,** 264-+.

LEVESQUE, J.-F., HARRIS, M. F. & RUSSELL, G. 2013. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *International journal for equity in health,* 12**,** 18.

MARMOT, M., ALLEN, J., BELL, R., BLOOMER, E. & GOLDBLATT, P. 2012. WHO European review of social determinants of health and the health divide. *The lancet,* 380**,** 1011-1029.

MCLAREN, Z. M., SHARP, A. R., ZHOU, J., WASSERMAN, S. & NANOO, A. 2017. Assessing healthcare quality using routine data: evaluating the performance of the national tuberculosis programme in South Africa. *Tropical Medicine and International Health,* 22**,** 171-179.

METCALFE, J. Z., MAKUMBIROFA, S., MAKAMURE, B., SANDY, C., BARA, W., MASON, P. & HOPEWELL, P. C. 2016. Xpert® MTB/RIF detection of rifampin resistance and time to treatment initiation in Harare, Zimbabwe. *The International Journal of Tuberculosis and Lung Disease,* 20**,** 882-889.

MNYAMBWA, N. P., LEKULE, I., NGADAYA, E. S., KIMARO, G., PETRUCKA, P., KIM, D.-J., LYMO, J., KAZWALA, R., MOSHA, F. & MFINANGA, S. G. 2018. Assessment of GeneXpert GxAlert platform for multi-drug resistant tuberculosis diagnosis and patients' linkage to care in Tanzania. *BMC research notes,* 11**,** 121.

MOHER, D., LIBERATI, A., TETZLAFF, J. & ALTMAN, D. G. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine,* 151**,** 264-269.

MOHR, E., DANIELS, J., MULLER, O., FURIN, J., CHABALALA, B., STEELE, S., COX, V., DOLBY, T., FERLAZZO, G. & SHROUFI, A. 2017. Missed opportunities for earlier diagnosis of rifampicin-resistant tuberculosis despite access to Xpert® MTB/RIF. *The International Journal of Tuberculosis and Lung Disease,* 21**,** 1100-1105.

MOYO, S., FURIN, J. J., HUGHES, J., DANIELS, J., SNYMAN, L., MULLER, O., COX, V., SHROUFI, A. & COX, H. 2014. Outcomes in adolescents undergoing treatment for drug-resistant tuberculosis in Cape Town, South Africa, 2008-2013. *Archives of Pediatric Infectious Diseases*.

MPAGAMA, S. G., HEYSELL, S. K., NDUSILO, N. D., KUMBURU, H. H., LEKULE, I. A., KISONGA, R. M., GRATZ, J., BOEREE, M. J., HOUPT, E. R. & KIBIKI, G. S. 2013. Diagnosis and interim treatment outcomes from the first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One,* 8**,** e62034.

NAIDOO, P., DU TOIT, E., DUNBAR, R., LOMBARD, C., CALDWELL, J., DETJEN, A., SQUIRE, S. B., ENARSON, D. A. & BEYERS, N. 2014a. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS One,* 9**,** e103328.

NAIDOO, P., TOIT, E. D., DUNBAR, R., LOMBARD, C., CALDWELL, J., DETJEN, A., SQUIRE, S. B., ENARSON, D. A. & BEYERS, N. 2014b. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and XpertReg. MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS ONE,* 9.

NAIDOO, P., VAN NIEKERK, M., DU TOIT, E., BEYERS, N. & LEON, N. 2015a. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests. *BMC health services research,* 15**,** 488.

NAIDOO, P., VAN NIEKERK, M., DU TOIT, E., BEYERS, N. & LEON, N. 2015b. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients’ experiences in the era of rapid molecular diagnostic tests. *BMC health services research,* 15**,** 488.

NKOSI, D., JANSSEN, S., PADANILAM, X., LOUW, R., MENEZES, C. N. & GROBUSCH, M. P. 2013. Factors influencing specialist care referral of multidrug- and extensively drug-resistant tuberculosis patients in Gauteng/South Africa: a descriptive questionnaire-based study. *BMC Health Services Research,* 13.

OGA-OMENKA, C., ZAROWSKY, C., AGBAJE, A., KUYE, J. & MENZIES, D. 2019. Rates and timeliness of treatment initiation among drug-resistant tuberculosis patients in Nigeria-A retrospective cohort study. *PloS one,* 14**,** e0215542.

OLIWA, J., MAINA, J., AYIEKO, P., GATHARA, D., KATHURE, I., MASINI, E., VAN’T HOOG, A., VAN HENSBROEK, M. & ENGLISH, M. 2018. Variability in distribution and use of tuberculosis diagnostic tests in Kenya: a cross-sectional survey. *BMC infectious diseases,* 18**,** 328.

ORGANIZATION, W. H. 2015. Gear up to end TB: introducing the end TB strategy. World Health Organization.

OSBORN, D., CUTTER, A. & ULLAH, F. Universal sustainable development goals. Understanding the transformational Challenge for Developed Countries. Report of Study by Stakeholder Forum, 2015.

PACE, R., PLUYE, P., BARTLETT, G., MACAULAY, A. C., SALSBERG, J., JAGOSH, J. & SELLER, R. 2012. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. *International journal of nursing studies,* 49**,** 47-53.

RASANATHAN, K., SIVASANKARA KURUP, A., JARAMILLO, E. & LÖNNROTH, K. 2011. The social determinants of health: key to global tuberculosis control. *The International Journal of Tuberculosis and Lung Disease,* 15**,** S30-S36.

REEVE, E., TO, J., HENDRIX, I., SHAKIB, S., ROBERTS, M. S. & WIESE, M. D. 2013. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs & aging,* 30**,** 793-807.

SCHAAF, H., SHEAN, K. & DONALD, P. 2003. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Archives of disease in childhood,* 88**,** 1106-1111.

STROBE STATEMENT. 2007. *STROBE Statement - Checklist of items that shouldbe included in reports of observational studies* [Online]. Available: https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf [Accessed 15 September 2018].

SULLIVAN, B. J., ESMAILI, B. E. & CUNNINGHAM, C. K. 2017. Barriers to initiating tuberculosis treatment in sub-Saharan Africa: a systematic review focused on children and youth. *Global health action,* 10**,** 1290317.
TIMIRE, C., SANDY, C., KUMAR, A. M., NGWENYA, M., MURWIRA, B., TAKARINDA, K. C. & HARRIES, A. D. 2019. Access to second-line drug susceptibility testing results among patients with Rifampicin resistant tuberculosis after introduction of the Hain® Line Probe Assay in Southern provinces, Zimbabwe. *International Journal of Infectious Diseases,* 81**,** 236-243.
TONG, A., SAINSBURY, P. & CRAIG, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International journal for quality in health care,* 19**,** 349-357.
UN 2018a. UN General Assembly High-Level Meeting on the fight against tuberculosis. New York: United Nations.
UN 2018b. UN General Assembly, Seventy-third session. *18th plenary meeting.* New York: United Nations.
VAN DE WATER, B. J., PRVU BETTGER, J., SILVA, S., HUMPHREYS, J., CUNNINGHAM, C. K. & FARLEY, J. E. 2017. Time to drug-resistant Tuberculosis treatment in a prospective South African Cohort. *Global pediatric health,* 4**,** 2333794X17744140.
VAN DEN HANDEL, T., HAMPTON, K., SANNE, I., STEVENS, W., CROUS, R. & VAN RIE, A. 2015. The impact of Xpert® MTB/RIF in sparsely populated rural settings. *The International Journal of Tuberculosis and Lung Disease,* 19**,** 392-398.
VAN DER WESTHUIZEN, H. & DRAMOWSKI, A. 2017. When students become patients: TB disease among medical undergraduates in Cape Town, South Africa. *South African Medical Journal,* 107**,** 475-479.
WHITTEMORE, R. & KNAFL, K. 2005. The integrative review: updated methodology. *Journal of advanced nursing,* 52**,** 546-553.
WHO 2007. Everybody's business--strengthening health systems to improve health outcomes: WHO's framework for action.
WHO 2014. Health in all policies: Helsinki statement. Framework for country action.
WHO 2015. Gear up to end TB: introducing the end TB strategy. World Health Organization.
WHO 2019. Global tuberculosis report 2019.
WORLD HEALTH ORGANIZATION 2014. Health in all policies: Helsinki statement. Framework for country action.
YANG, W.-T., GOUNDER, C. R., AKANDE, T., DE NEVE, J.-W., MCINTIRE, K. N., CHANDRASEKHAR, A., DE LIMA PEREIRA, A., GUMMADI, N., SAMANTA, S. & GUPTA, A. 2014. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberculosis research and treatment,* 2014.
ZAROWSKY, C., HADDAD, S. & NGUYEN, V.-K. 2013. Beyond 'vulnerable groups': contexts and dynamics of vulnerability. *Global Health Promotion,* 20**,** 3-9.
ZIMRI, K., HESSELING, A. C., GODFREY-FAUSSETT, P., SCHAAF, H. S. & SEDDON, J. A. 2012. Why do child contacts of multidrug-resistant tuberculosis not come to the assessment clinic? *Public Health Action,* 2**,** 71-75.

Supplementary Files - Article 1

PICO Elements

Quality Assessment Results

Quality Assessment Checklists

Weighted Ranking of Access Factors

1A: PICO Elements

PICO Aspect	Description	Key Terms
Population	Individuals eligible for drug-resistant TB testing and treatment	(multi-drug resistant tuberculosis or drug resistant tuberculosis or tuberculosis or pulmonary tuberculosis or Mycobacterium tuberculosis or MDR or MDRTB or DRTB or DR-TB)
Intervention	Any studies on the factors influencing diagnosis or treatment for DR-TB	(Health seeking or care-seeking or health care delivery or case detection or case finding or diagnosis or treatment initiation or patient cost* or transport cost* or socio-demograph* or socio-economic* or place of residence or rural or distance or age or sex or knowledge or perception or gender or presentation)
Comparator	Not applicable or as defined in the included studies, where applicable	
Outcome	Delay or missed opportunities in diagnosis and or treatment for DR-TB.	(provider barriers or patient barriers or health system barriers or missed diagnosis or untreated or diagnostic delay or late diagnosis or delay in diagnosis or access to diagnosis or diagnostic errors or undiagnosed or case diagnosis or early diagnosis or late presentation)
Setting	Sub-Saharan African countries	(Africa or SSA or sub-saharan Africa or Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cabo Verde or Cameroon or Central African Republic or Chad or Comoros or Democratic Republic of the Congo or Republic of the Congo or Cote d'Ivoire or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Libya or Madagascar or Malawi or Mali or Mauritania or Mauritius or Morocco or Mozambique or Namibia or Niger or Nigeria or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or South Sudan or Sudan or Swaziland or Tanzania or Togo or Tunisia or Uganda or Zambia or Zimbabwe)
Study design	Original, primary quantitative, qualitative and mixed studies	
Time period	Between January 2006 and July 2019	

1B: Quality Assessment Results

Annex 2: Quality Assessment Results

References	Item																																T	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32		
Qualitative Studies																																		
1. Bieh 2017	1	0	0	1	0	1	1	1	0	1	1	1	1	1	0	0	1	0	1	0	1	0	0	1	0	1	1	0	1	1	1	1	20	B
2. Naidoo 2015	1	0	1	1	0	1	1	1	0	1	1	1	1	1	0	1	1	1	1	0	0	1	0	1	1	1	0	0	1	1	1	1	23	A
Quantitative Studies																																		
3. Cox 2015	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	0	0	0	0	1	0	0	1	1	0	1	1	1			19	B
4. Cox 2017	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1			26	A
5. Dlamini-Mvelase 2014	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	0	1	1	1	0	0	1	1	1	1	1	1	1	0			24	A
6. Ebonwu 2013	1	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1			22	A
7. Evans 2018	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1			25	A
8. Hanrahan 2012	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	0		1	1	1	1	1	1	1			24	A
9. Hanrahan 2013	0	1	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1			24	A
10. Iruedo 2017	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	0	1	0	1	1	1	1	1	1	1	1			26	A
11. Jacobson 2012	1	1	1	1	1	1	1	0	1	0	1	1	1	0	1	1	0	1	1	0	1	0	1	1	1	1	1	0	0	1			22	A
12. Jacobson 2017	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1			26	A
13. Jokwiro 2018	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	0	0	0	1	1	1	1	1	1	1			22	A
14. Kweza 2018	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0			27	A
15. McLaren 2017	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	1			18	B
16. Metcalfe	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	1	1	1	1	1	0	1	1	1	1	1	1	1			24	A
17. Mohr 2017	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0			24	A
18. Moyo	0	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	1	0		1	1	1	1	1	1	1			22	A
19. Naidoo 2014	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	1	1	1	0	1	1	0	1	1	1	1	1			23	A
20. Nkosi 2013	1	1	1	1	1	1	1	1	1	0	1	1	1	0	0	0	0	1	1	0	0	1	1	1		1	1	1	1	0			21	A
21. Oga-Omenka 2019	1	1	1	1	1	1	1	1	1	0	1	1	1		1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1			26	A
22. Oliwa 2018	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	1	0	0	1	1	0	1	1	1	1	1	1	0			22	A
23. Timire 2019	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	0	1	0	1	1	0	1	1	1	1	1	1	1	1			24	A
24 Van Den Handel 2015	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	0	1	0	0	1	0	0	1	1	1	1	1	1	1			23	A

References	Item																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	T	
Mixed Methods Studies																																		
25. Doulla 2019	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1																15	A
26. Mpagama 2019	0	1	0	1	1	0	0	1	1	1	0	1	1	1	1	0	1																11	B
27. Mnyambwa 2018	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0																13	A
28. Weshuizen 2017	1	1	1	1	1	0	1	1	0	1	0	1	1	1	1	0	1																13	A
29. Zimri	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0																15	A

Grade	0=Unclear; 1=Clear

1C: WEIGHTED RANKING OF FACTORS

Annex 3: Weighted Ranking of Access Factors

BARRIERS						
Factor	Study #	Score	Number of studies with factor	Average scores	Final Rank	Comment if result not obvious or mixed methods
Provider factors						
	21	3				Stated in results and table 2
Guidelines non-availability	1	3	2	3.0	6	
	23	3				
	27	3				
	26	3				
	27	3				Mentioned separately in qualitative part of mixed methods
Infrastructure and equipment: coverage and coverage	2	3	5	3.0	15	
	20	3				
Decentralization	26	2	2	2.5	5	
	13	3				
	24	3				
	26	3				
	27	1				25% and 18% affected by this barrier
	28	3				
	29	2				Reasons for this delay not given
	3	3				
	26	3				
Laboratory operational issues	27	1	9	2.4	22	Mentioned separately in qualitative part of mixed methods
	3	3				
Clinic operational issues: waiting times	29	2	2	2.5	5	

Factor	Study #	Score	Number of studies with factor	Average scores	Final Rank	Comment if result not obvious or mixed methods
Provider factors						
	21	3				
	3	3				
Clinic operational issues: patient tracking and follow up	27	2	3	2.7	8	Odds ratio in Table 3 and mentioned in results
	7	3				
Level of care- higher level	23	1	2	2.0	4	Odds ratio in Table 3 and mentioned in results
	23	3				
	29	3				
Private sector care: low index of suspicion, poor linkage	3	3	3	3.0	9	
	13	3				
	16	2				
	24	2				
	27	3				
Rural location: differrences in testing, capacity and referral	26	2	5	2.4	12	
	2	3				
	26	3				
Inadequate staff strength	27	1	3	2.3	7	
	5	3				
	13	2				
	18	3				
	21	3				
	23	2				
	24	2				
Non-adherence to care guidelines	3	2	7	2.4	17.0	
	6	2				
	27	3				
	29	3				
	1	2				
	3	2				
	26	3				
Inadequate HCW knowledge, training and experience	30	2	7	2.4	17.0	

Factor	Study #	Score	Number of studies with factor	Average scores	Final Rank	Comment if result not obvious or mixed methods
Provider factors						
	2	3				
Poor HCW attitude, motivation including stigma and discrimination	27	2	2	2.5	5	
	18	2				
	22	2				
	28	3				
	26	3				
Poor data management	27	1	5	2.2	11	
	10	3				
	20	3				
Older diagnostics and timeliness	26	3	3	3.0	9	
	4	2				
	25	3				Table 2 and discussion
	5	3				
Inadequate impact of newer diagnostics on rates of diagnosis or treatment	20	3	4	2.8	11	
	29	2				
Inadequate availability to testing or testing materials	27	3	2	2.5	5	
Inadequate access to second line drugs	1	3	1	3	3	
Initial negative or invalid tests	3	3	1	3	3	
	1	2				
Inadequate availability to testing or testing materials	29	3	2	2.5	5	
Patient factors						
	15	3				
	11	2				
	13	2				
Female gender*	30	3	4	2.5	10	
	5	2				
	13	2				
Younger patient age*	23	3	3	2.3	7	
Pregnancy	3	3	1	3	3	
	10	3				
	3	3				
HIV negative status or fear of HIV diagnosis*	23	3	3	3.0	9	
	13	3				
Fewer presenting symptoms**	15	3	2	3	6	

Factor	Study #	Score	Number of studies with factor	Average scores	Final Rank	Comment if result not obvious or mixed methods
Patient factors						
Lifestyle: cigarette smoking	30	3	1	3	3	
Ethnicity	30	3	1	3	3	
	30	3				
	3	3				
Negative patient perception	28	3	3	3.0	9	
	2	3				
Self denial and non-disclosure	3	3	2	3	6	
	29	2				
	3	3				
	29	2				
Family, school or work commitments	30	2	4	2.3	9	
	7	3				
	21	3				
	28	2				
	19	2				
Loss to follow-up or death	28	3	5	2.6	13	
	7	3				
	12	3				
Less urban or informal residence and certain regions	22	2	3	2.7	8	
	30	3				
	3	2				
Transportation difficulty	29	2	3	2.3	7	
	1	2				
High costs of care	29	2	2	2	4	
Treatment refusal	19	2	1	2	2	
	27	2				
	3	1				
Use of alternative care	27	1	3	1.3	4	

FACILITATORS						
Factor	Study #	Score	Number of studies with factor	Average scores	Final Rank	Comment if result not obvious or mixed methods
Provider factors						
	16	1				
Guideline availability, inclusion and awareness campaigns	9	3	2	2.0	4	
Infrastructure and equipment: technology improving communication	28	2	1	2	2	
	4	3				In the discussion
	10	3				
	8	3				
	19	3				
	24	3				
	25	3				
Decentralization	3	2	7	2.9	20	Listed in Table 1
Laboratory operational issues: expedited mail services	26	2	1	2	2	
	5	3				
	19	3				
	22	2				
Level of care- lower level , TB clinic or in-patient care	16	3	4	2.8	11	
	23	3				
Public sector care	3	3	2	3.0	6	
	5	2				
	13	3				
	14	3				
Urban location: differences in testing, capacity and referral	24	3	4	2.8	11	

Factor	Study #	Score	Number of studies with factor	Average scores	Final Rank	Comment if result not obvious or mixed methods
Provider factors						
HCW knowledge, training and experience	27	3				
	3	2				Listed in Table 1
	26	3	3	2.7	8	
HCW motivation and attitude	3	3	1	3	3	
Newer diagnostics and timeliness to diagnosis and treatment	10	3				
	4	3				
	5	3				
	9	3				
	11	3				
	12	3				
	20	3	7	3.0	21	
Newer diagnostics on rates of diagnosis or treatment	8	3	1	3	3	
Increased access to testing	8	3	1	3	3	
Patient factors						
Older patient age*	15	3				
	23	3	2	3.0	6	
HIV positive status*	10	3				
	23	3				
	3	3	3	3.0	9	
More presenting symptoms**	15	3				
	23	3				
	3	2	3	2.7	8	
Patient agency and knowledge	3	3	1	3	3	
Family support	3	2	1	2	2	
City or semi-urban residence	7	2				
	22	3	2	2.5	5	

1D: Checklists of Quality Assessment Questions for Qualitative, Quantitative and Mixed Methods

A Quality Assessment of Qualitative Studies using the Consolidated criteria for reporting qualitative research (COREQ), 2015	
Domain 1: Research team and reflexivity	
Personal Characteristics	
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?
2. Credentials	What were the researcher's credentials? E.g. PhD, MD
3. Occupation	What was their occupation at the time of the study?
4. Gender	Was the researcher male or female?
5. Experience and training	What experience or training did the researcher have?
Relationship with participants	
6. Relationship established	Was a relationship established prior to study commencement?
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic
Domain 2: study design	
Theoretical framework	
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis
Participant selection	
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email
12. Sample size	How many participants were in the study?
13. Non-participation	How many people refused to participate or dropped out? Reasons?
Setting	
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace
15. Presence of non-participants	Was anyone else present besides the participants and researchers?
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date
Data collection	
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?
20. Field notes	Were field notes made during and/or after the interview or focus group?

21. Duration	What was the duration of the interviews or focus group?
22. Data saturation	Was data saturation discussed?
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?
Domain 3: analysis and findings	
Data analysis	
24. Number of data coders	How many data coders coded the data?
25. Description of the coding tree	Did authors provide a description of the coding tree?
26. Derivation of themes	Were themes identified in advance or derived from the data?
27. Software	What software, if applicable, was used to manage the data?
28. Participant checking	Did participants provide feedback on the findings?
Reporting	
29. Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number
30. Data and findings consistent	Was there consistency between the data presented and the findings?
31. Clarity of major themes	Were major themes clearly presented in the findings?
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?
TOTAL (out of 32 possible points)	
Grade	0=Unclear; 1=Clear

A Quality Assessment of Mixed Method Studies using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), 2007	
Title and abstract	
	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction	
1. Background/ rationale	Explain the scientific background and rationale for the investigation being reported
2. Objectives	State specific objectives, including any prespecified hypotheses
Methods	
3. Study design	Present key elements of study design early in the paper
4. Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection

5. Participants	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants
	(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case
6. Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
7. Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
8. Bias	Describe any efforts to address potential sources of bias
9. Study size	Explain how the study size was arrived at
10. Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
11. Statistical methods	(a) Describe all statistical methods, including those used to control for confounding
12	(*b*) Describe any methods used to examine subgroups and interactions
13	(*c*) Explain how missing data were addressed
14	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
15	(*e*) Describe any sensitivity analyses
Results	
16. Participants	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
17	(b) Give reasons for non-participation at each stage
18	(c) Consider use of a flow diagram
19. Descriptive data	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
20	(b) Indicate number of participants with missing data for each variable of interest
	(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
21. Outcome data	Cohort study—Report numbers of outcome events or summary measures over time

	Case-control study—Report numbers in each exposure category, or summary measures of exposure
	Cross-sectional study—Report numbers of outcome events or summary measures
22. Main results	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
23	(b) Report category boundaries when continuous variables were categorized
24	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
25. Other analyses	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion	
26. Key results	Summarise key results with reference to study objectives
27. Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
28. Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
29. Generalisability	Discuss the generalisability (external validity) of the study results
Other information	
30. Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
Score /30	
Grade	0=Unclear; 1=Clear

A Quality Assessment of Mixed Method Studies using the Mixed Methods Appraisal Tool (MMAT), 2018	
Screening questions (for all types)	
1	S1. Are there clear research questions?
2	S2. Do the collected data allow to address the research questions?
1. Qualitative	
3	1.1. Is the qualitative approach appropriate to answer the research question?
4	1.2. Are the qualitative data collection methods adequate to address the research question?
5	1.3. Are the findings adequately derived from the data?
6	1.4. Is the interpretation of results sufficiently substantiated by data?

7	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?
2. Quantitative randomized controlled trials	
8a	2.1. Is randomization appropriately performed?
9a	2.2. Are the groups comparable at baseline?
10a	2.3. Are there complete outcome data?
11a	2.4. Are outcome assessors blinded to the intervention provided?
12a	2.5 Did the participants adhere to the assigned intervention?
3. Quantitative non- randomized	
8b	3.1. Are the participants representative of the target population?
9b	3.2. Are measurements appropriate regarding both the outcome and exposure/intervention?
10b	3.3. Are there complete outcome data?
11b	3.4. Are the confounders accounted for in the design and analysis?
12b	3.5. During the study period, is the intervention/exposure administered as intended?
4. Quantitative descriptive	
8c	4.1. Is the sampling strategy relevant to address the research question?
9c	4.2. Is the sample representative of the target population?
10c	4.3. Are the measurements appropriate?
11c	4.4. Is the risk of nonresponse bias low?
12c	4.5. Is the statistical analysis appropriate to answer the research question?
5. Mixed methods	
13	5.1. Is there an adequate rationale for using a mixed methods design to address the research question?
14	5.2. Are the different components of the study effectively integrated to answer the research question?
15	5.3. Are the results adequately brought together into overall interpretations?
16	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?
17	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?
Score /17	
Grade	0=Unclear; 1=Clear

Article 2: Qualitative Meta-Synthesis

Title page

Title: A qualitative meta-synthesis of facilitators and barriers to tuberculosis diagnosis and treatment in Nigeria

Authors and affiliations:

Charity Oga-Omenka [1,2,3], Lawrence Wakdet[4], Dick Menzies[3,5], Christina Zarowsky[1,2,6]

1. School of Public Health of the University of Montreal (ESPUM), Canada
2. Centre de recherche en santé publique, Université de Montréal (CReSP), Canada
3. McGill University International TB Centre, Montreal, Quebec, Canada
4. Institute of Human Virology Nigeria, Kano, Nigeria
5. Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada
6. School of Public Health, University of the Western Cape, South Africa

Conflicts of interest, author contributions and funding: clearly described: None declared

Corresponding author:

Charity Oga-Omenka

Running head: Facilitators and barriers to TB care in Nigeria

Declarations: Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests: The authors declare they have no competing interests

Status: This article was submitted to BMC Public Health in July 2020 and recommended for publication following revisions. In this revision, most of the reviewers' comments have been addressed but these have not yet been reviewed by the co-authors.

DOI: 10.21203/rs.3.rs-39365/v1

Abstract

Background

Despite progress in tuberculosis (TB) control globally, TB continues to be a leading cause of death from infectious diseases, claiming 1.2 million lives in 2018; 214,000 of these deaths were due to drug resistant strains. Of the estimated 10 million cases globally in 2018, 24% were in Africa, with Nigeria and South Africa making up most of these numbers.

Nigeria ranks 6th in the world for TB burden, with an estimated 4.3% multi-drug resistance in new cases. However, the country had one of the lowest case detection rates, estimated at 24% of incident cases in 2018 - well below the WHO STOP TB target of 84%. This rate highlights the need to understand contextual issues influencing tuberculosis management in Nigeria. Our synthesis was aimed at synthesizing qualitative evidence on factors influencing TB care in Nigeria.

Methods

A three-stage thematic meta-synthesis of qualitative studies was used to identify barriers and facilitators to tuberculosis case finding and treatment in Nigeria. A search of eleven databases was conducted. The date of publication was limited to 2006 to June 2020. We analyzed articles using a three-stage process, resulting in coding, descriptive subthemes and analytical themes.

Results

Our final synthesis of 10 articles resulted in several categories including community and family involvement, education and knowledge, attitudes and stigma, alternative care options, health system factors (including coverage and human resource), gender, and direct and indirect cost of care. These were grouped into three major themes: individual factors; interpersonal influences; and health system factors.

Conclusion

Case finding and treatment for TB in Nigeria currently depends more on individual patients presenting voluntarily to the hospital for care, necessitating an understanding of patient behaviors towards TB diagnosis and treatment. Our synthesis has identified several related factors that shape patients' behavior towards TB management at individual, community and

health system levels that can inform future interventions.

Keywords

TB case finding, TB treatment, Nigeria, qualitative meta-synthesis, barriers and facilitators

Background

Tuberculosis (TB) remains a global leading cause of death from a single infectious disease, infecting 10 million and killing an estimated 1.2 million people in 2018 (WHO, 2019a). It is caused by the bacillus *Mycobacterium tuberculosis*, and spread through minute droplets produced through coughing or sneezing (Riley et al., 1959, Riley, 1957). It typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB) (WHO, 2019a). People infected with the human immunodeficiency virus (HIV) are more prone to TB disease due to a weakened immune system (WHO, 2019a, Mckenna, 1992).

The drug resistant (DR) form is resistant to rifampicin or to both isoniazid and rifampicin, the common anti-TB medications. it requires lengthy treatment with multiple, potentially toxic drugs that are up to five times costlier, and results in poorer treatment outcomes (WHO, 2019a, EUI, 2019, WHO, 2017c, WHO, 2018c). Much of DR-TB results from human-made errors including poor management of drug-susceptible (DS-) TB infections, delayed, inadequate access or substandard TB medications, or poor adherence (Pai, 2019, WHO, 2014a). DR-TB, estimated at 4.3% of new cases, was estimated to have claimed 214,000 lives in 2018 (WHO, 2019a). The mixture of high incidence rates of both TB and human immunodeficiency virus (HIV) infections in sub-Saharan Africa adds new levels of complications to diagnosis, emphasizing the need for coordinated and effective control strategies (Adebisi et al., 2020, WHO, 2019a).

TB case detection and access to medications are proven interventions in reducing the TB burdens of countries and are critical to meeting the global strategies to end TB. Several global initiatives have set targets towards ending the TB epidemic by 2030. In September 2018, the United Nations held its first high-level meeting on TB with the goal of ending the TB epidemic by 2030, in line with the Sustainable Development Goal (SDG) Target 3.3 (UN, 2018a). The WHO End TB Strategy 2016-2035 aims to reduce TB deaths by 90%, reduce new cases by 80% and ensure no family faces catastrophic costs due to TB (WHO, 2019a). The 90-90-90 Stop TB target aims to reach 90% of all people with TB, 90% of key populations while keeping a 90% treatment success rate (WHO, 2019a).

In Nigeria, TB is a major public health problem. The WHO estimated the burden of TB in Nigeria in 2018, with 429,000 incident cases, to be the highest in Africa (and 6th highest globally) and resulting in 157,000 deaths (WHO, 2019a). However, the 2018 case notification and treatment rates for all forms of TB at only 24%, were among the lowest in the world (WHO, 2019a). Lack of access to healthcare and failure of healthcare workers to recognize symptoms and test for TB in patients are among some of the reasons for underdiagnosis of TB (WHO, 2019a). Additionally, a survey of TB patients in Nigeria revealed one of the highest catastrophic health costs (71%) among other high burden countries, mostly due to direct non-medical costs (transportation, lodging, and nutritional supplements) (WHO, 2019a). All these factors point to significant barriers in access to diagnosis and treatment in Nigeria, even though diagnosis and treatment for all forms of TB is provided for free (Ukwaja et al., 2013b).

The Nigerian TB Control Program has declared finding the missing TB cases as the most important priority for TB control for the upcoming years (NBLCP/FMOH., 2019). In order to meet any of these targets, there is an urgent need to understand contextual issues influencing TB management in Nigeria (NBLCP/FMOH., 2019, WHO, 2019a, WHO, 2010a).

Several studies from Nigeria have identified barriers to TB care access (Abimbola et al., 2015, Ibrahim et al., 2014a, Ukwaja et al., 2013a, Ukwaja et al., 2013d), with only a few using qualitative design. The use of qualitative research is particularly necessary to thoroughly understand the contexts, complex relationships and patterns at play (Pope and Mays, 1995) at the different points in a patient's pathway to TB care, as well as the perspectives and behaviors of patients and health providers and the complex relations in health care systems, and how these constitute barriers to TB diagnosis and treatment (Engel and Pai, 2013, Ngamvithayapong-Yanai, 2016). A synthesis of qualitative research is useful in exploring questions about why interventions work or do not, and in what context; what the barriers and facilitators are to accessing health care and the impact of these on people, their behaviors and experiences (Higgins, 2008). In order to understand the contextual factors that influence access to care, there is a need to bring together, summarize and explore new meanings from the available qualitative data (Erwin et al., 2011, Walsh and Downe, 2005, Barratt et al., 2016).

Our systematic review of qualitative studies explores the barriers and facilitators of TB healthcare in Nigeria using a meta-synthesis approach (Thomas and Harden, 2008). The research question guiding this meta-synthesis is: What does qualitative research tell us about the barriers and facilitators to TB care in Nigeria?

Methods

Overview

Our thematic synthesis explored barriers and facilitators to TB programs at the individual, community and at the health system levels (McLeroy et al., 1988, Golden and Earp, 2012). The steps in a meta-synthesis involve identifying the research question and relevant studies, appraising the studies for quality and synthesizing the studies (Williams, 2016). After the process of literature selection and quality assessment, this study applied a thematic approach to qualitative meta-synthesis, as described by Thomas and Harden (Thomas and Harden, 2008). The thematic synthesis is applied in three steps beginning with the creation of codes from the original study findings, further organization into descriptive subthemes and finally development of analytical themes (Barnett-Page and Thomas, 2009, Thomas and Harden, 2008).

Step 1: Identifying the Research Question

Our research question aligns with the operational and public health research priorities of the WHO International Roadmap for TB Research and the Nigerian TB Program to target barriers to scale-up of TB care and scale up notification and treatment (World Health Organization Stop TB, 2011, NBLCP/FMOH., 2019, NTBLCP, 2014). The WHO identified these priorities through review of evidence, expert meetings and consultations with stakeholders and working groups of the Stop TB partnership (World Health Organization Stop TB, 2011).

The research question was framed using the **SPIDER** approach as recommended by Cooke et al (Cooke et al., 2012):

- **Sample**: Tuberculosis patients in Nigeria
- **Phenomenon of Interest**: Access to diagnosis and treatment of TB

- **Design**: Meta-synthesis of research using interviews, focus group discussions, observation, in-depth or key informant interviews
- **Evaluation**: The reported barriers and facilitators
- **Research type**: Qualitative research

Our SPIDER-generated research question: *What does qualitative research tell us about the barriers and facilitators to diagnosis and treatment access for TB patients in Nigeria?*

Step 2: Data sources and identification

We created a search strategy by identifying four key themes in the research question: tuberculosis, access, qualitative and Nigeria. 'Search terms and variations were generated based on the themes. These can be seen in the *Figure 6*: Medline Search Strategy.

1	Tuberculosis, Pulmonary/ Or Mycobacterium Tuberculosis/ Or Tuberculosis/ Or Latent Tuberculosis/ Or Tuberculosis, Multidrug-Resistant/ Or Extensively Drug-Resistant Tuberculosis/
2	limit 1 to yr="2016 -Current"
3	(delay or barrier or diagnostic error* or access or late).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	limit 3 to yr="2016 -Current"
5	(qualitative or interview$ or focus group$ or phenomenology or ethnograph$ or grounded theory or observation$ or field stud$ or case stud$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	limit 5 to yr="2016 -Current"
7	NIGERIA/
8	limit 7 to yr="2016 -Current"
9	2 and 4 and 6 and 8

Figure 6. – Medline Search Strategy

Eleven databases searched were searched- Medline, Scopus, EBM Review, Web of Science, Pubmed, Embase, CINAHL, Global Health, African Journal Online (AJOL), the International Journal for TB and Lung Disease (IJLTD) and Google Scholar. A reference list search for included studies did not yield any additional study. Search results were exported to EndNote®. The date of publication was limited from January 2006 (2006 being the 1st publication year for the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis*) to the date of search, which was 18th of August 2018. The search was rerun on the 30th of June 2020. There were no language restrictions.

Step 3: Study selection and quality assessment

The citations imported into Endnote® were screened in a stepwise approach starting with removal of duplicates, followed by the review of titles, abstracts, and finally the full text based on the inclusion and exclusion criteria. This process is shown in *Figure 7*.

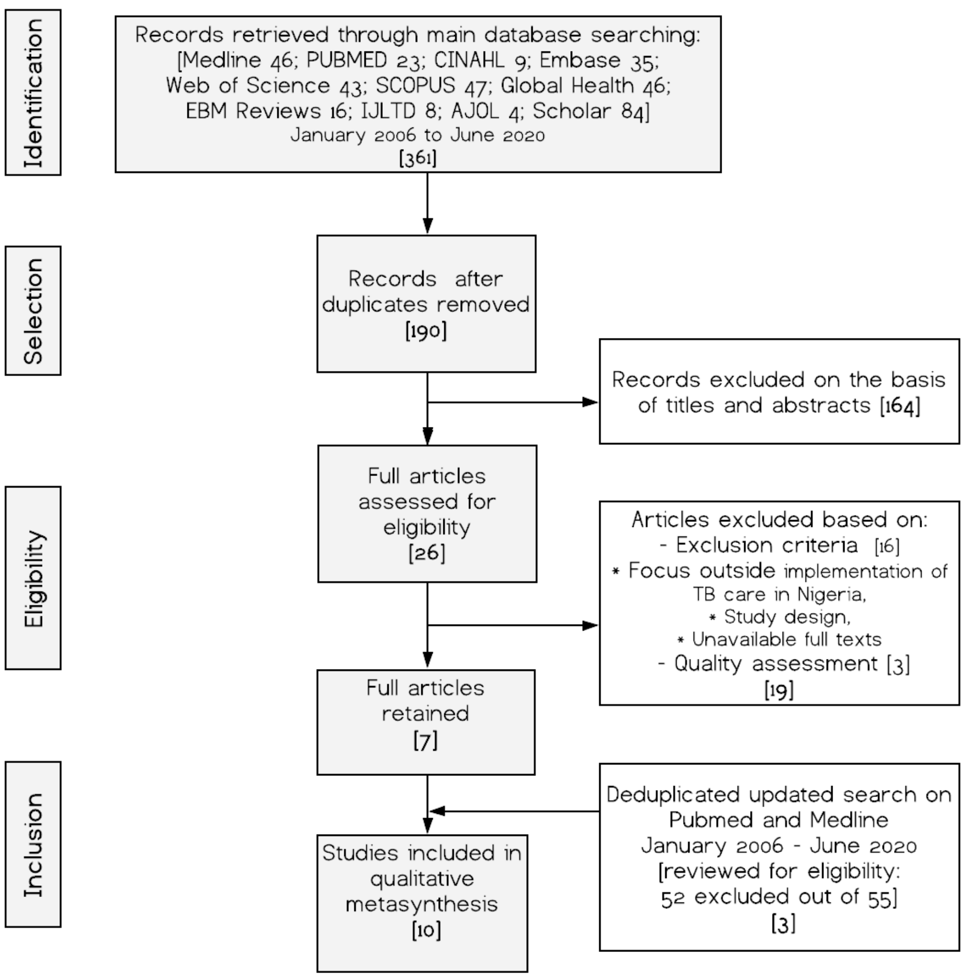


Figure 7. – PRISMA Diagram of Selection Process

Inclusion criteria

- Studies focusing on case finding and treatment of TB in Nigeria
- Studies published from 2006 to June 2020
- All languages

Exclusion criteria

- Abstracts without full texts
- Focus outside Nigeria
- Not peer reviewed
- Absence of qualitative data

A quality assessment was performed independently by two authors (COO and LW), using the simplified criteria for qualitative research, recommended by Murphy et al (Murphy et al., 1998). This involved two initial criteria and seven screening questions to determine the credibility and relevance of the studies (Murphy et al., 1998, Salter et al., 2008). Results of the quality assessments were discussed, and differences resolved by consensus.

Step 4: Thematic Synthesis

As described by Thomas and Harden, the process of a thematic synthesis has three stages – free line-by-line coding of the text within the 'Results' sections of the primary studies, creation of descriptive subthemes by organizing the codes into related areas, and finally, the generation of analytical themes across the set of retained studies (Thomas and Harden, 2008). The descriptive subthemes are similar to that found in the primary studies, but the analytical themes represent the new interpretation generated from those (Ring et al., 2011, Thomas and Harden, 2008, Barnett-Page and Thomas, 2009). All texts of results were read, line after line, and the content of each text fragment interpreted. All sentences were then copied into the Quirkos database, except for one, (Ajayi et al., 2013), which examined community initiatives for health interventions and not just for TB. For this, only sections within the results that were relevant for TB disease were selected. The next step was a sentence-by-sentence coding base on meaning and content, with some sentences getting more than one code. This process resulted in a total of 21 initial codes. The process of developing the descriptive subthemes involved looking at the similarities and differences between the codes and grouping them into a hierarchical tree structure. New terms were used to describe the meanings and contexts of groups of initial codes. This process resulted in a hierarchical structure with a total of 10 descriptive subthemes. Three analytical or 'higher order' (Cruzes and Dyba, 2011) themes were created by interpreting the relationships between themes across studies and in relation to the research question. This was done using the Quirkos software.

Results

Study characteristics

There were 10 studies from Nigeria that explored factors that impact access to TB care from a qualitative perspective, 9 qualitative studies and 1 mixed method. The characteristics of the 10 studies synthesized are presented in Table 4.

Table 4 ***Overview of selected studies***

	First Author, Year	Title	Data collection	Method of data analysis	Main themes
1	Adejumo, 2020	Challenges of Tuberculosis Control in Lagos State, Nigeria: A Qualitative Study of Health-Care Providers' Perspectives	34 in-depth interviews with health workers	Data coded deductively into previously identified themes	Challenges with TB management and supervision, laboratory tests, DOTS providers' training, and work overload
2	Ajayi, 2013	Assessing resources for implementing a community directed intervention (CDI) strategy in delivering multiple health interventions in urban poor communities in Southwestern Nigeria: a qualitative study	12 Focus group discussions and 73 key informant interviews (KIIs) with stakeholders	Content analysis-inductive and deductive	Community resources can facilitate access to health care
3	Bieh, 2017	Hospitalized care for MDR-TB in Port Harcourt, Nigeria: a qualitative study	2 gender based FGDs and 11 in-depth interviews with patients	Transcription of data, coding and thematic assembly and analysis	Patient-centered care improves access and removes stigma
4	Ogbuabor, 2020	Through service providers' eyes: health systems factors affecting implementation of tuberculosis control in Enugu State, South Eastern Nigeria	23 in-depth interviews with health workers	Framework approach	Leadership and governance, health financing and human resources, supply chain system (technology), health information system and service delivery
5	Olukolade, 2017	Role of treatment supporters beyond monitoring daily drug intake for TB-patients: Findings from a qualitative study in Nigeria	2 FGDs, 15 KIIs and IDIs	Data transcription and content analysis	Patient nominated treatment supporter and patient centered approach to TB Therapy very crucial
6	Okeibunor, 2007	Barriers to care seeking in directly observed therapy short-course (DOTS) clinics and tuberculosis control in southern Nigeria: a qualitative analysis	24 in-depth interviews & 24 FGDs	Themes were developed in the form of codes and further summarized ethno-graphically	Perceived causes of TB infection, perceived high costs & quality of care prevent patients from accessing available services

7	Onyeneho, 2010	Is there a role for patent medicine vendors (PMVs) in tuberculosis control in southern Nigeria?	17 interviews each with PMV and community leaders	Developing, describing and interpreting codes	Knowledge and practice about TB, referral practices, awareness of TB clinics, involvement in detection of TB cases and attitudes towards involvement of PMVs in TB control
8	Oshi, 2016	Gender-related factors influencing women's health seeking for tuberculosis care in Ebonyi state, Nigeria	56 interviews – with 46 women and 10 men from 6 communities	Cross-case analysis of key themes	Socio-cultural & economic factors weaken women's access to health care
9	Ushie, 2012	The paradox of family support: Concerns of tuberculosis-infected HIV patients about involving family and friends in their treatment.	8 FGD, 21 In-depth Interviews, 4Case histories	Thematic analysis	Family support promotes adherence
10	Ukwaja et al (2017)	Sustaining the DOTS': stakeholders' experience of a social protection intervention for TB in Nigeria.	103 key Informant interview, 2 FGD, 10 In-depth interviews	Thematic content analysis until data saturation	Patients and health workers recorded positive outcomes with financial inducements

A variety of methods were used in data collection including in-depth interviews, focus group discussions, semi-structured interviews and key informant interviews. Sample size ranged from 24 to 221.

The ten studies differed in focus even though all directly or indirectly explored factors influencing diagnosis and treatment to care- including barriers to direct observable treatment short course (DOTS), the WHO endorsed system of TB care (Okeibunor et al., 2007, Adejumo et al., 2020, Ukwaja et al., 2017, Olukolade et al., 2017); the role of family members (Ushie and Jegede, 2012, Bieh et al., 2017b, Okeibunor et al., 2007, Oshi et al., 2016a), patent medicine vendors (PMVs) (Onyeneho and Chukwu, 2010) and treatment supporters (Olukolade et al., 2017); particular focus on gender-based factors (Oshi et al., 2016a), care pathways (Okeibunor et al., 2007), challenges of drug-resistant TB care (Bieh et al., 2017b) and TB/HIV co-infection (Ushie and Jegede, 2012); as well as community-level interventions with some particular reference to TB (Ajayi et al., 2013).

Quality assessment

The quality assessment for the selected studies are presented in *Table 5*. Three (3) out of ten studies were classified as "A", and the remaining 8 classified as "B", using the Murphy criteria (Murphy et al., 1998).

Table 5: ***Quality Assessment***

Study	Credibility					Relevance		Score
	Data collection	Auditability	Reflexivity	Negative cases	Fair dealing	Transferability	Analytic generalization	
Adejumo 2020	x	x				x	x	B
Ajayi 2013	x	x	x		x	x	x	A
Bieh et al, 2017	x	x	x		x	x	x	A
Ogbuabor 2020	x	x			x	x	x	B
Olukolade et al., 2017	x	x			x	x		B
Okeibunor et al, 2006	x	x			x	x	x	B
Onyeneho 2010	x	x			x	x	x	B
Oshi et al, 2016	x	x			x	x	x	B
Ushie & Jegede 2012	x	x			x	x	x	B
Ukwaja et al 2017	x	x	x		x	x	x	A
1-2 points = C, 3-5 points = B and 6-7 points = A								

Quality assessment questions

Credibility

Data collection • Were explanations of sampling strategies and data collection methods provided?

Auditability • Was the method of data analysis described and enough data displayed to allow the reader to determine whether the interpretations made by the researcher is supported by the data?

Reflexivity • Did the authors acknowledge the influence of the research process and the presence of the researcher including the role of prior biases, assumptions and experience, on the collected data?

Negative cases • Has appropriate attention been given to contradictory data? Are negative cases taken into account?

Fair dealing • Did the authors explore alternative, plausible explanations for the data collected and incorporate a range of different perspectives?

Relevance

Transferability • Did the authors provide information regarding participants, setting and context so that the reader might be able to determine the relevance of the findings to other settings (transferability)?

Analytic generalization	• Did the authors discuss findings within a broader context, propose generalization of findings and/or suggest a direction for future research?	

Synthesis of results

Description of themes

Our synthesis yielded three main themes and eleven inter-related sub-themes *(Figure 2).* On the individual level, financial capacity, education and knowledge, as well as attitudes and beliefs were facilitators or barriers. On the interpersonal level, family influences and community involvement were facilitators, while negative community attitudes and beliefs, especially towards public sector TB care, and harmful gender norms, were barriers. At the facility level, cost of service, human resource and coverage and type of services were either facilitators or barriers. We also discuss the stage of care - diagnosis or treatment – the access factor was more prevalent.

Each of the three themes are presented in more detail below.

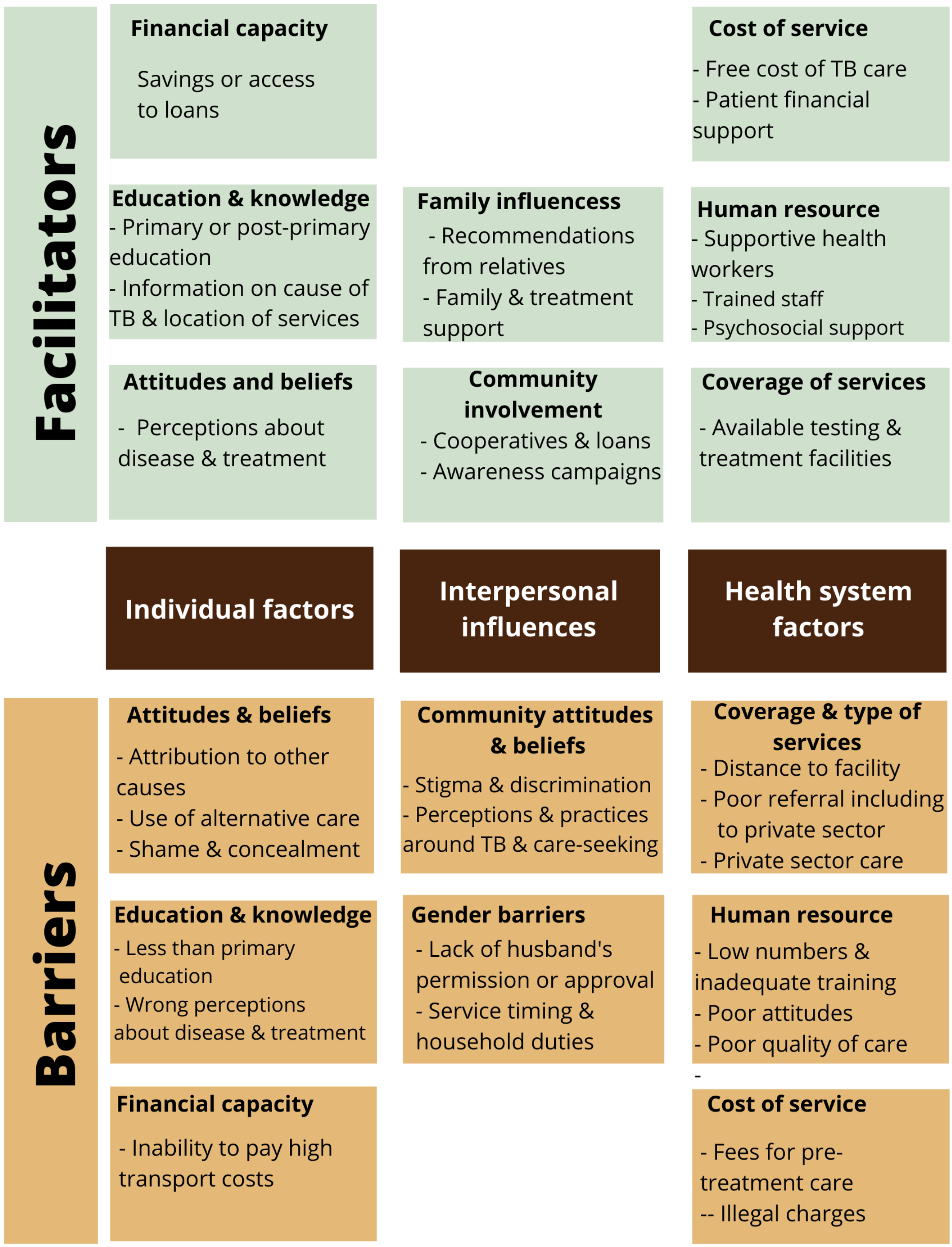


Figure 8. – Diagram showing barriers and facilitators associated with each theme and subthemes

Individual factors

This theme reflects the individual-level factors that determine the use of healthcare. It emanated from three descriptive subthemes of financial capacity, education and knowledge, attitudes and beliefs.

Cost of treatment, particularly indirect costs e.g. related to transport or illegally charged fees, were cited by participants as a major barrier to both diagnosis and treatment.

"Efficacy and cost of treatment are topmost. Also, the attitude of health staff is a major issue. Although treatment is said to be free, health workers extort money from patients" (FGD with women who live far from clinic) (Okeibunor et al., 2006).

"There are very few women in my community who can afford the costs of transportation to the hospital and to pay the hospital fees. Maybe the traders! Even then, if they are not cautious taking money from their business to go for treatment will spoil [ruin] their business..." (Interview with 29 years old female with secondary education) (Oshi et al., 2016b).

"Many women go to faith healers now not because they do not know that it is better to have treatment in the hospital, but because they cannot afford it. Many of our women are not employed …"(Ajayi et al., 2013).

However, patients who received family support, as discussed below, were better able to mitigate the cost barrier.

Several codes related to the patient's education and knowledge, attitudes and beliefs were particularly harmful to correct diagnosis, which participants noted in retrospect. Knowledge about the cause of TB or the availability of free care, negative perceptions of public sector care or a preference for alternative care in the private sector were recurring barriers to diagnosis.

"It is only a prophet who can destroy the powers of the witch. So, such persons who have TB can only be cured through prayers by powerful prophets" (41 years old female, uneducated farmer)

(Oshi et al., 2016b).

'It took some time before I went to get drugs for this illness... I went to two prayer houses yet I did not get better ...so I started taking herbal treatment' (FGD, 42-year-old male) (Ukwaja et al., 2017).

For some patients, the use of alternative treatments, or the reason for delayed care-seeking were due to financial constraints. This was a particular barrier to diagnosis.

"*For the first two months when I started coughing, it was very hard for me because I had no money to go to the chemist... even after I visited the chemist and got some drugs the cough persisted*" (FGD, 65-year-old male) (Ukwaja et al., 2017).

"*I did not have any money to buy drugs when my illness started...so I started taking herbal remedies*" (FGD, 58-year- old female) (Ukwaja et al., 2017).

Some of these factors were inter-related, for example uneducated patients were more likely to delay treatment in favor of prayer houses and traditional healers.

"Health seeking depends on the level of education. The [uneducated] would delay going to hospital. They first use local herbs." "Patients first move to chemists and herbalists and finally hospital if they cannot get cure from these sources. Where they go first depends on whether they believe TB is man-made, natural, or caused by witchcraft." (Okeibunor et al., 2006).

A few patients complained about the fact that most available health resources in their immediate localities were focused on pregnant women and children, alienating males and other women. This perception of public healthcare could have been a barrier to diagnosis, especially for males.

"All the health programmes in this community are designed for women and children. Is there nothing that can be done for adult males and females? If we are sick and not treated, we will transfer the sickness to the children (Ajayi et al., 2013).

Interpersonal influences

This theme refers to the effect of the family and community on the decision-making processes of people in need of care, ranging from codes on stigma and discrimination to community awareness campaigns. It is also reflected in the extent of deference women were expected to have towards their husbands when it comes to health seeking decisions.

Factors like stigma and discrimination affected women differently from men, as some participants were quoted saying a female TB patient would be a pariah and would be unlikely to get suitors or could possibly be divorced as a result of her illness. Also, a husband who attribute TB to other causes or who have negative perceptions about its management could potentially prevent his wife from accessing care.

"Women should be submissive to their husbands. A woman who knows more than her husband portends danger to the community. If a man says the medicine is good, then it is good. If he says the medicine is not good, who is the wife to disagree." (MUA, elderly, female, non-literate, farmer) (Oshi et al., 2016b).

"… The ability of a woman to pay for hospital treatment does not mean that she can just get up and go to the hospital without her husband's permission." (Oshi et al., 2016b).

"The community leader… argued that traditionally, infection with TB is not grounds for divorce, but spouses often cloak the real reason for seeking separation. . ." (Okeibunor et al., 2006).

On the other hand, family and community support were facilitators to initiating and adhering to treatment. This support was sometimes financial and this enabled patients to continue accessing treatment.

"For me it was very traumatic to start taking drugs I have not been used to... but I got so many encouragements, people around me, ... And probably to be frank, if not for their own encouragement and everything, I would have stopped; because this is my last month, I wouldn't have taken it this far, I would have stopped, but they encouraged me that I had to complete the period of medication" Female TB Patient, Asokoro (Olukolade et al., 2017).

"*My son and wife have been very helpful...they accompany and support me to go to the clinic and to take my drugs"* (IDI, 50-year-old male) (Ukwaja et al., 2017).

"*Whenever I am seating lonely and quiet, my husband usually comes to me and asks: 'why am I seating quiet, am I alright? And whenever my drugs are finished, he goes and gets them for me and he advises me to take the drugs*", Female TB Patient Interview, (Olukolade et al., 2017).

"My difficulty is getting transportation to get to this place (DOTS centre). I will go and meet my brother to tell him that I am supposed to go and take drugs then he will find me some money for transportation", Male TB Patient (Olukolade et al., 2017).

For some, having a knowledgeable person in the community, sometimes healthcare workers, direct them to the right public facility for TB care were facilitators of diagnosis.

"*I visited all the chemists in my community and took several medication, yet the cough kept increasing...I visited the health centre twice before the nurse said I may have TB I should come to this hospital*" (IDI, 35-year-old female) (Ukwaja et al., 2017).

Health system factors

Health system barriers were a recurring theme in all the studies. They emerged from codes around poor coverage of services, weak referral system, low numbers and poor skills in health workers, poor attitude of staff and quality of care, corrupt staff demanding illegal charges from patients and the relatively high cost of patient cards. These codes were grouped into 3 descriptive subthemes- coverage and type of services, human resource, and cost of service.

Coverage and opening hours were cited as barriers, mostly to diagnosis but sometimes in relation to treatment access.

"If they [hospitals] want to help us they should make their opening hours flexible so that we [women] can also go there in the evening hours, after the days' work. That will be more convenient for women." (Oshi et al., 2016b).

Poor coverage was also linked to high transportation costs and the reason why patients were choosing alternative care in the private sector. These were mostly barriers to diagnosis.

"There is no general hospital around. The nearest one … is far from here. Many people don't want to go there because of cost of the transportation and services. People treat themselves at home or go to herbalists. Only very few people go to private hospitals as they are very expensive (Ajayi et al., 2013).

The attitude of healthcare workers created barriers to diagnosis for a number of patients.

"Both health workers and herbalists have the same attitude. In the hospital you pay for cards, the herbalist demand money for entering the bush. However, in the hospital the much-trumpeted free treatment is not true because health workers demand money " (Okeibunor et al., 2006) .

""Even some nurses and medical workers treated us like we are not fit to live again. They keep a distance when they want to communicate with us. If you come closer, they will shout go! go!! go!!! .... The feeling of stigma is very difficult. I felt like the worst person on earth having MDR-TB" (IDI, 29 years old male (Bieh et al., 2017a).

"…. I have been sending my patients for a laboratory test at a particular hospital, but she refused to go because of the way she was treated the last time she went. I decided to visit the place myself to see with my eyes what was going on. You cannot imagine what I saw. Immediately they (the health workers) saw me approaching them, they shouted at me to go back as I walked in not knowing I am a DOTS Provider. I can imagine what the patients go through…." (DOTS Provider) (Adejumo et al., 2020).

Healthcare workers, on their part, complained of shortage of workers, unbearable workloads, inadequate training and a lack of laboratory resources. These challenges were mostly barriers to diagnosis, and sometimes to treatment as well.

"*…For me as an example, I am the clinician in my facility. I am expected to go on outreach[es], consultation of patients that come to my facility is my responsibility. I am the DOTS provider. I used to have 22, now I have 27 centers under me to supervise. Then how do I share myself,…*"

(TB Supervisor) (Adejumo et al., 2020).

"*My workload is high. It is not only TB services that I provide. I am also the anti-retroviral therapy focal person*" (Ogbuabor, 2020).

Patent medicine vendors are readily available in the communities and see a lot of clients with coughs. However, many PMVs were not trained on TB control nor were aware of TB DOTS centers but were overwhelmingly eager to be part of the TB control effort (Onyeneho and Chukwu, 2010). The use of alternative care in the private sector was always a barrier, due to the poor linkage between the public and private sector. Several reasons contributed to the use of the PMVs and some of these linked back to individual factors. They included poor coverage of health services, patients in geographical locations with poor accessibility where only PMVs were available, perceived high costs of care in the public sector, even though TB services were supposedly free.

"Patent medicine vendors are the main source of healthcare service delivery in this community. Many people go to PMVs because medicines are not readily available at the health centres and if available, they are costlier because patients have to pay for other services such as a consultation when they go to the hospital" (Ajayi et al., 2013).

"We are in the local communities, a very interior part of the community, and we deal with people of the local communities; hence, such people come to the patent medicine shop to re-quest, "sir, do you have something like this" (PMV practitioner) (Onyeneho and Chukwu, 2010)

Some of the PMVs were not aware of how to diagnose TB or the availability of free TB services in the public healthcare system.

"*… I have not heard about it (DOTS clinic). I am not aware of DOTS clinic but if it is evolved, it will help in the control of people with tuberculosis in our environment*" Interview with an official of a local PMV association (Onyeneho and Chukwu, 2010).

"They (PMVs) should be informed, involved, educated, and trained.... You will know what you

have learnt, and if anything comes up, you will tell the person" (PMV leader) (Onyeneho and Chukwu, 2010).

Other factors that were mentioned include absence of doctors at community levels and illegal charges demanded from patients. Several patients alleged that healthcare workers were diverting free medications from the TB centres to their private health centres, where they now charge the patients. As this was mainly from one article, we were not able to ascertain if this problem was widespread.

"*Attitude of health workers, cost and distance are the issues here. Health workers at the DOTS clinics can hardly be seen, sometimes for a month or more. The health workers have their private Chemists/consulting shops where they treat their private patients. They sometimes divert clinic resources for that purpose*" (FGD with women) (Okeibunor et al., 2006).

"*Health workers at DOTS clinic, all have consulting shops outside the hospital. Drugs are not free. Attitude of health workers toward patients is influenced by amount of money the patient has*" (FGD with men) (Okeibunor et al., 2006).

Key facilitators included the financial support provided to the patient by the program.

"I thank you for providing us this money...most times when I want to come to the hospital I borrow money for transportation then when I collect the money I will go and pay back" (IDI, 45-year-old female) (Ukwaja et al., 2017).

Discussion

This meta-synthesis looked at barriers and facilitators to TB diagnosis and treatment in Nigeria and resulted in three major themes, centered on individual, interpersonal influences, and health systems factors. These themes were common across different studies, irrespective of type of study and data collection method. They were also inter-related even though presented here separately. The findings of this synthesis are in line with several other studies, within and outside Nigeria.

For example, studies on TB control in Nigeria show operational challenges occurring at patient and health system levels. Reported barriers include beliefs about causes of TB, knowledge of treatment duration and benefits, socioeconomic status, literacy, stigma, hidden treatment costs, distance from the clinic, access to health care, and health worker attitude and knowledge (Ibrahim et al., 2014a, Erah and Ojieabu, 2009).

Specifically, other studies and reviews, including from elsewhere in Africa, identify *patient level* barriers as cost of care, fear of stigma, distance from facility, worsening disease, inadequate knowledge about the disease, and perceptions of poor quality of care at hospitals (Belard et al., 2015, Engel et al., 2015, Naidoo et al., 2013, Naidoo et al., 2014a, Naidoo et al., 2015b, Storla et al., 2008). Facilitators to patient TB care-seeking behavior have been identified in literature as knowledge of TB and HIV disease and treatment (Cox et al., 2015, Naidoo et al., 2015b).

At the *community level*, other studies also identified awareness and screening campaigns as facilitators (Basu et al., 2009, Cox et al., 2015, Gilbert et al., 2015). These agree with findings of studies from several African studies in Zimbabwe, Malawi and Ethiopia, where active case finding in the community, e.g. using mobile vans to be very effective even in communities in close proximity to a hospital (WHO, 2015e, Corbett et al., 2010, Golub et al., 2005a, Floyd et al., 2003, Datiko and Lindtjørn, 2009, Yassin et al., 2013a).

At the *health system level*, barriers like poor tracking of patients, delays in access to testing, staff shortages and work overload/overtime, inadequate health worker knowledge of transmission, misdiagnosis, poor infection control, staff shortages, overwhelming workloads, additional testing required and lengthy triage procedures have been identified (Basu et al., 2009, Biadglegne et al., 2014, Cox et al., 2015, Engel et al., 2015, Ettehad et al., 2012, Falzon et al., 2013, Loveday et al., 2008, Naidoo et al., 2013, Naidoo et al., 2014a).

On the other hand, facilitators in health systems are patient financial support, quick testing time, appropriate counseling and testing, patient tracking, health worker training, quick and efficient workflows, sufficient staffing, free and confidential TB services (Basu et al., 2009, Belard et al., 2015, Cox et al., 2015, Engel et al., 2015, Naidoo et al., 2015b, O'Hara et al., 2015, Tudor et al., 2014, Oshi et al., 2019).

Authors of selected articles made several recommendations for tackling identified barriers. These included training, supervision and logistical support for healthcare workers, as well as resource mobilisation and hiring of new health workers (Adejumo et al., 2020, Okeibunor et al., 2006, Ogbuabor, 2020); training and engagement of patent medicine dealers by the National TB program (Onyeneho and Chukwu, 2010); financial, family and community support, as well as home-based care wherever possible for patients (Olukolade et al., 2017, Ukwaja et al., 2017, Bieh et al., 2017a, Ushie and Jegede, 2012, Ajayi et al., 2013); women empowering policies, programmes and interventions targeting harmful gender norms with the aim of increasing women's access to TB services (Oshi et al., 2016b).

Meta-synthesis limitation:

The main limitation of our study is that we chose to include most of the studies that met our inclusion criteria, sometimes in spite of quality, and low methodological rigor. This was done to include as much available data as possible, due to a low availability of qualitative research on barriers to TB care from Nigeria. As a result of this, the identified themes are subject to the limitations, rigor and quality of the original articles. This may limit the transferability of our findings. However, we ensured that all selected studies had relevant data on barriers to TB care in Nigeria. Another limitation is the sparsity of data relating to several aspects of TB care identified in literature as being more difficult, including pediatric or drug-resistant TB diagnosis and treatment.

CONCLUSIONS

This synthesis highlights a number of factors influencing access to diagnosis and treatment of TB in Nigeria, including attitudes and beliefs, financial capacity, education and knowledge on the individual level; community attitudes and beliefs, family influences, including negative gender norms, community involvement and private sector care on the community level; and coverage, human resource and cost of service on the health system level.

Based on these findings, interventions are needed to improve case finding, for example, increasing patient education and community awareness to modify harmful perceptions on TB disease and management. This could potentially improve diagnosis and treatment rates by reducing the time and expenses spent by patients seeking care outside facilities equipped to diagnose and treat TB cases in Nigeria. Also, measures are needed to improve health worker attitudes and the quality of care they provide.

References

ADEBISI, Y. A., AGUMAGE, I., SYLVANUS, T. D., NAWAILA, I. J., EKWERE, W. A., NASIRU, M., OKON, E. E., EKPENYONG, A. M. & LUCERO-PRISNO III, D. E. 2020. Burden of tuberculosis and challenges facing its eradication in West Africa. *target,* 4.

ADEJUMO, O. A., DANIEL, O. J., ADEPOJU, V. A., FEMI-ADEBAYO, T., ADEBAYO, B. I. & AIRAUHI, A. O. 2020. Challenges of Tuberculosis Control in Lagos State, Nigeria: A Qualitative Study of Health-Care Providers' Perspectives. *Niger Med J,* 61**,** 37-41.

AJAYI, I. O., JEGEDE, A. S., FALADE, C. O. & SOMMERFELD, J. 2013a. Assessing resources for implementing a community directed intervention (CDI) strategy in delivering multiple health interventions in urban poor communities in Southwestern Nigeria: a qualitative study. *Infect Dis Poverty,* 2**,** 25.

AJAYI, I. O., JEGEDE, A. S., FALADE, C. O. & SOMMERFELD, J. 2013b. Assessing resources for implementing a community directed intervention (CDI) strategy in delivering multiple health interventions in urban poor communities in Southwestern Nigeria: a qualitative study. *Infectious diseases of poverty,* 2**,** 25.

ANDERSON, K., STOWASSER, D., FREEMAN, C. & SCOTT, I. 2014. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ open,* 4**,** e006544.

BARNETT-PAGE, E. & THOMAS, J. 2009a. Methods for the synthesis of qualitative research: a critical review. *BMC medical research methodology,* 9**,** 1-11.

BARNETT-PAGE, E. & THOMAS, J. 2009b. Methods for the synthesis of qualitative research: a critical review. *BMC medical research methodology,* 9**,** 1.

BASU, S., FRIEDLAND, G. H., MEDLOCK, J., ANDREWS, J. R., SHAH, N. S., GANDHI, N. R., MOLL, A., MOODLEY, P., STURM, A. W. & GALVANI, A. P. 2009. Averting epidemics of extensively drug-resistant tuberculosis. *Proceedings of the National Academy of Sciences of the United States of America,* 106**,** 7672-7677.

BELARD, S., JANSSEN, S., OSBAK, K. K., ADEGNIKA, A. A., ONDOUNDA, M. & GROBUSCH, M. P. 2015. Limited access to drugs for resistant tuberculosis: a call to action. *Journal of Public Health,* 37**,** 691-693.

BIADGLEGNE, F., SACK, U. & RODLOFF, A. C. 2014. Multidrug-resistant tuberculosis in Ethiopia: Efforts to expand diagnostic services, treatment and care. *Antimicrobial Resistance and Infection Control,* 3.

BIEH, K. L., WEIGEL, R. & SMITH, H. 2017. Hospitalized care for MDR-TB in Port Harcourt, Nigeria: a qualitative study. *BMC Infect Dis,* 17**,** 50.

BRADLEY, E. H., CURRY, L. A. & DEVERS, K. J. 2007. Qualitative data analysis for health services research: developing taxonomy, themes, and theory. *Health services research,* 42**,** 1758-1772.

COOKE, A., SMITH, D. & BOOTH, A. 2012. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qualitative health research,* 22**,** 1435-1443.

CORBETT, E. L., BANDASON, T., DUONG, T., DAUYA, E., MAKAMURE, B., CHURCHYARD, G. J., WILLIAMS, B. G., MUNYATI, S. S., BUTTERWORTH, A. E. & MASON, P. R. 2010. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *The Lancet,* 376**,** 1244-1253.

COX, H. S., DANIELS, J. F., MULLER, O., NICOL, M. P., COX, V., VAN CUTSEM, G., MOYO, S., DE AZEVEDO, V. & HUGHES, J. 2015. Impact of Decentralized Care and the Xpert MTB/RIF Test on Rifampicin-Resistant Tuberculosis Treatment Initiation in Khayelitsha, South Africa. *Open Forum Infectious Diseases,* 2.

CRUZES, D. S. & DYBA, T. Recommended steps for thematic synthesis in software engineering. 2011 International Symposium on Empirical Software Engineering and Measurement, 2011. IEEE, 275-284.

DATIKO, D. G. & LINDTJØRN, B. 2009. Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. *PloS one,* 4**,** e5443.

ENGEL, N., DAVIDS, M., BLANKVOORT, N., PAI, N. P., DHEDA, K. & PAI, M. 2015. Compounding diagnostic delays: A qualitative study of point-of-care testing in South Africa. *Tropical Medicine and International Health,* 20**,** 493-500.

ENGEL, N. & PAI, M. 2013. Tuberculosis diagnostics: why we need more qualitative research. *Journal of epidemiology and global health,* 3**,** 119-121.

ERAH, P. & OJIEABU, W. 2009. Success of the control of tuberculosis in Nigeria: A Review. *International Journal of Health Research,* 2.

ETTEHAD, D., SCHAAF, H. S., SEDDON, J. A., COOKE, G. S. & FORD, N. 2012. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infectious Diseases,* 12**,** 449-456.

FALZON, D., JARAMILLO, E., WARES, F., ZIGNOL, M., FLOYD, K. & RAVIGLIONE, M. C. 2013. Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. *Lancet Infectious Diseases,* 13**,** 690-697.

FLOYD, K., SKEVA, J., NYIRENDA, T., GAUSI, F. & SALANIPONI, F. 2003. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. *The International Journal of Tuberculosis and lung disease,* 7**,** S29-S37.

GILBERT, J. A., LONG, E. F., BROOKS, R. P., FRIEDLAND, G. H., MOLL, A. P., TOWNSEND, J. P., GALVANI, A. P. & SHENOI, S. V. 2015. Integrating community-based interventions to reverse the convergent TB/HIV epidemics in rural South Africa. *PLoS ONE,* 10.

GOLDEN, S. D. & EARP, J. A. L. 2012. Social ecological approaches to individuals and their contexts: twenty years of health education & behavior health promotion interventions. *Health education & behavior,* 39**,** 364-372.

GOLUB, J., MOHAN, C., COMSTOCK, G. & CHAISSON, R. 2005. Active case finding of tuberculosis: historical perspective and future prospects. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease,* 9**,** 1183.

HIGGINS, J. P. 2008. Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration. http://www. *cochrane-handbook. org*.

IBRAHIM, L. M., HADEJIA, I. S., NGUKU, P., DANKOLI, R., WAZIRI, N. E., AKHIMIEN, M. O., OGIRI, S., OYEMAKINDE, A., DALHATU, I., NWANYANWU, O. & NSUBUGA, P. 2014. Factors associated with interruption of treatment among Pulmonary Tuberculosis patients in Plateau State, Nigeria. 2011. *The Pan African medical journal,* 17**,** 78.

LOVEDAY, M., THOMSON, L., CHOPRA, M. & NDLELA, Z. 2008. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. *International Journal of Tuberculosis and Lung Disease,* 12**,** 1042-1047.

MCLEROY, K. R., BIBEAU, D., STECKLER, A. & GLANZ, K. 1988. An ecological perspective on health promotion programs. *Health education quarterly,* 15**,** 351-377.

MURPHY, E., DINGWALL, R., GREATBATCH, D., PARKER, S. & WATSON, P. 1998. Qualitative research methods in health technology assessment: a review of the literature.

NAIDOO, A., NAIDOO, S., GATHIRAM, P. & LALLOO, U. 2013. Tuberculosis in medical doctors - a study of personal experiences and attitudes. *Samj South African Medical Journal,* 103**,** 176-180.

NAIDOO, P., DU TOIT, E., DUNBAR, R., LOMBARD, C., CALDWELL, J., DETJEN, A., SQUIRE, S. B., ENARSON, D. A. & BEYERS, N. 2014. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS ONE,* 9.

NAIDOO, P., VAN NIEKERK, M., DU TOIT, E., BEYERS, N. & LEON, N. 2015. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests. *Bmc Health Services Research,* 15.

NBLCP/FMOH 2014. The National Strategic Plan for Tuberculosis Control: Towards Universal Access to Prevention, Diagnosis and Treatment- 2015-2020. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH. 2019. 2019 Annual TB Report. *In:* PROGRAMME., N. T. A. L. C. (ed.). Nigeria:.

NGAMVITHAYAPONG-YANAI, J. 2016. The role of qualitative research in ending TB. *Public Health Action,* 6**,** 209.

O'HARA, N. N., ROY, L., O'HARA, L. M., SPIEGEL, J. M., LYND, L. D., FITZGERALD, J. M., YASSI, A., NOPHALE, L. E. & MARRA, C. A. 2015. Healthcare Worker Preferences for Active Tuberculosis Case Finding Programs in South Africa: A Best-Worst Scaling Choice Experiment. *Plos One,* 10.

OKEIBUNOR, J. C., ONYENEHO, N. G., CHUKWU, J. N. & POST, E. 2007. Barriers to care seeking in directly observed therapy short-course (DOTS) clinics and tuberculosis control in southern Nigeria: a qualitative analysis. *International quarterly of community health education,* 27**,** 23-37.

OLUKOLADE, R., HASSAN, A., OGBUJI, Q., OLUJIMI, S., OKWUONYE, L., KUSIMO, O., OKECHUKWU, J., OSHO, J., OSINOWO, K. & LADIPO, O. 2017. Role of treatment supporters beyond monitoring daily drug intake for TB-patients: findings from a qualitative study in Nigeria. *Journal of Public Health and Epidemiology,* 9**,** 65-73.

ONYENEHO, N. G. & CHUKWU, J. N. 2010. Is there a role for patent medicine vendors in tuberculosis control in southern Nigeria? *Journal of health, population, and nutrition,* 28**,** 567.

ORGANIZATION, W. H. 2010. The global plan to stop TB 2011-2015: transforming the fight towards elimination of tuberculosis.

OSHI, D., CHUKWU, J., NWAFOR, C., CHUKWU, N. E., MEKA, A. O., ANYIM, M., UKWAJA, K. N., ALOBU, I., EKEKE, N. & OSHI, S. N. 2019. Support and unmet needs of patients undergoing multidrug-resistant tuberculosis (MDR-TB) treatment in southern Nigeria. *Int J Health Plann Manage*.

OSHI, D. C., OSHI, S. N., ALOBU, I. N. & UKWAJA, K. N. 2016a. Gender-related factors influencing women's health seeking for tuberculosis care in Ebonyi State, Nigeria. *Journal of Biosocial Science,* 48**,** 37-50.

OSHI, D. C., OSHI, S. N., ALOBU, I. N. & UKWAJA, K. N. 2016b. Gender-related factors influencing women's health seeking for tuberculosis care in Ebonyi State, Nigeria. *J Biosoc Sci,* 48**,** 37-50.

POPE, C. & MAYS, N. 1995. Qualitative research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *Bmj,* 311**,** 42-45.

RING, N. A., RITCHIE, K., MANDAVA, L. & JEPSON, R. 2011. A guide to synthesising qualitative research for researchers undertaking health technology assessments and systematic reviews.

SALTER, K., HELLINGS, C., FOLEY, N. & TEASELL, R. 2008. The experience of living with stroke: a qualitative meta-synthesis. *Journal of rehabilitation medicine,* 40**,** 595-602.

STORLA, D. G., YIMER, S. & BJUNE, G. A. 2008. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC public health,* 8**,** 1.

THOMAS, J. & HARDEN, A. 2008. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC medical research methodology,* 8**,** 45.

TUDOR, C., VAN DER WALT, M., MARGOT, B., DORMAN, S. E., PAN, W. K., YENOKYAN, G. & FARLEY, J. E. 2014. Tuberculosis among health care workers in KwaZulu-Natal, South Africa: a retrospective cohort analysis. *Bmc Public Health,* 14.

UKWAJA, K. N., ALOBU, I. & HOPEWELL, P. C. 2013. The high cost of free tuberculosis services: patient and household costs associated with tuberculosis care in Ebonyi State, Nigeria. *PloS one,* 8**,** e73134.

UKWAJA, K. N., ALOBU, I., MUSTAPHA, G., ONAZI, O. & OSHI, D. C. 2017. 'Sustaining the DOTS': stakeholders' experience of a social protection intervention for TB in Nigeria. *International Health,* 9**,** 112-117.

UN 2018. UN General Assembly High-Level Meeting on the fight against tuberculosis. New York: United Nations.

USHIE, B. A. & JEGEDE, A. S. 2012. The paradox of family support: concerns of tuberculosis-infected HIV patients about involving family and friends in their treatment. *AIDS patient care and STDs,* 26**,** 674-680.

WHO 2015. Global tuberculosis report 2015.

WILLIAMS, T. L., & SHAW, R. L. 2016. Synthesizing qualitative research. *In:* (EDS.)., S. (ed.) *International handbook of qualitative methods in sport and exercise.* London: Routledge.

WORLD HEALTH ORGANIZATION 2019. Global tuberculosis report 2019.

WORLD HEALTH ORGANIZATION STOP TB 2011. Partnership. An international roadmap for tuberculosis research. *Geneva, Switzerland: WHO*.

YASSIN, M. A., DATIKO, D. G., TULLOCH, O., MARKOS, P., ASCHALEW, M., SHARGIE, E. B., DANGISSO, M. H., KOMATSU, R., SAHU, S. & BLOK, L. 2013. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. *PloS one,* 8**,** e63174.

CHAPTER 4 – METHODOLOGY

4.1 Study Design

This study utilized an explanatory sequential transformative mixed method design (Creswell and Plano Clark, 2011). A mixed methods approach involves collecting and analyzing, integrating findings, and drawing conclusions using quantitative and qualitative data (Teddlie and Tashakkori, 2009). When combined, quantitative and qualitative methods are complementary and yield a deeper understanding of a phenomenon, and are ideal for investigating multiple, inter-related objectives. Data generated from each objective were needed to inform, validate or clarify other objectives (Teddlie and Tashakkori, 2009, Creswell and Clark, 2007, Creswell, 2013). The objectives of this study required different methods that needed to be examined together to give a deeper understanding of the problem of low diagnosis and treatment rates of DR-TB in Nigeria.

We used a transformative design which involves a theoretical lens to guide interpretation (Creswell and Clark, 2007, Creswell, 2013). The main goal of transformative research is to advocate for social justice and address power imbalances on the basis of rigorous research, by focusing on inequalities and marginalization, and this is reflected in every stage of the research (Mertens, 2007, Sweetman et al., 2010). "*Transformative mixed methods research is needed because research does not necessarily serve the needs of those who have traditionally been excluded from positions of power in the research world, and therefore the potential to further human rights through a research agenda has not been fully realized. The transformative paradigm provides such a framework for examining assumptions that explicitly address power issues, social justice, and cultural complexity throughout the research process*" (Mertens, 2007) (p 212-213).

The overarching theoretical framework guiding this transformative study is the concept of equity of access to healthcare (Goddard and Smith, 2001, Levy and Sidel, 2013, Levesque et al., 2013). Inequalities in access to health involves failures in access to services based on needs, as well as in appropriate health services for the same needs, irrespective of the socio-demographic characteristics of the individuals (Almgren, 2018, Goddard and Smith, 2001, Levy and Sidel, 2013). The theoretical framework, discussed in Chapter 2, was also considered through the lens of the continuum of care cascade, which is a model for assessing patient retention across a series of stages in care that individuals must navigate to achieve a successful disease outcome (Subbaraman et al., 2019b).

This study started with a mixed methods literature review, beginning in 2016. The preliminary results from the both the mixed methods systematic review and the meta-synthesis of qualitative results were used to design the initial interview tools and to develop and adapt a conceptual framework.

This was followed by an empirical study in two phases. This explanatory sequential mixed method study began with an initial quantitative followed by a qualitative phase to explain the initial quantitative phase (Creswell et al., 2003, Sweetman et al., 2010, Ivankova et al., 2006). The quantitative phase investigated health system and patient factors influencing diagnosis and treatment, as well as the gaps in the DR-TB care continuum. This was followed by a qualitative phase exploring contextual reasons behind these identified and other factors influencing access to care, from the perspectives of patients, treatment supporters and providers.

In the first phase of the empirical study, a retrospective database and patient chart analysis was done to explore the relationships between socio-demographic characteristics of sex, age and geographic location, with treatment initiation, and time to treatment.

We also utilized National and World Health Organization (WHO)'s estimates for prevalence to construct a 5-year care cascade in Nigeria between 2013 and 2017. Using a cascade model helped to measure gaps and pinpoint areas for improvement in access to DR-TB care.

Using a qualitative embedded case study approach (Yin, 2013), the second phase included focus group discussions (FGDs) and key informant interviews (KIIs) to explore the dynamics of access to healthcare services from the experiences and perspectives of patients, their relatives and treatment supporters, as well as healthcare workers in 3 different States implementing hospital and community-based DR-TB care in Nigeria. Program managers at the State and Federal levels were also interviewed. The qualitative phase also included a documentary analysis of DR-TB policies, of guidelines and workers manuals.

The quantitative data provided an overview of the research problem, focusing more on sociodemographic characteristics associated with diagnosis and timely treatment, while the qualitative data explored the statistically significant results in more detail, and delved further by probing for other factors influencing care.

The two phases were integrated in two stages: first during the development of the qualitative interview questions and selection of participants and location for the case study; and, again, in the interpretation and discussion of results

The visual model showing procedures for the study using sequential transformative mixed methods, as recommended by Ivanokovka, 2006 is shown in *Figure 9* (Ivankova et al., 2006).

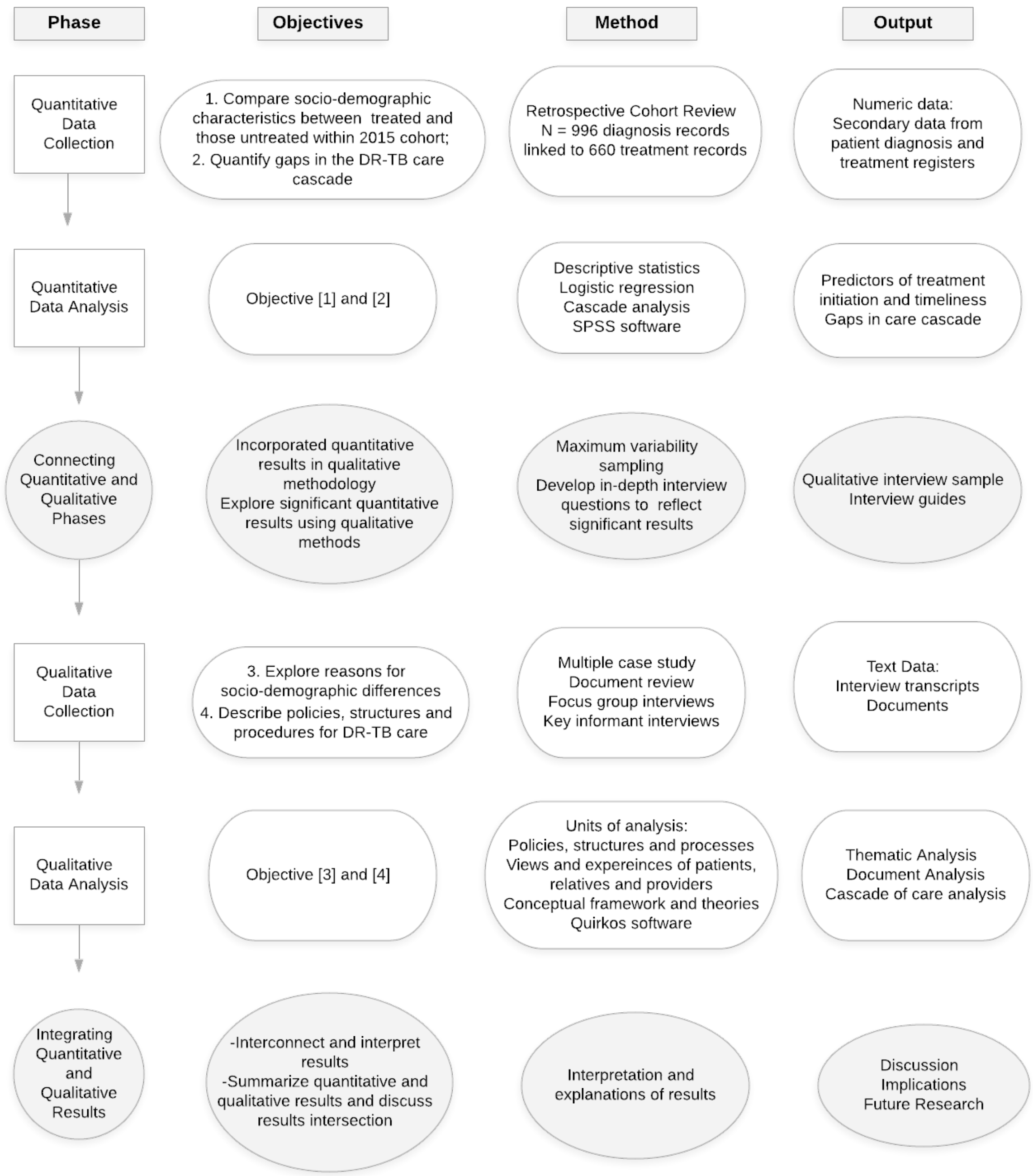


Figure 9. – Visual model showing sequential transformative mixed-methods procedure

4.2 Methods for the quantitative phase

The full details of the quantitative methods are detailed in articles 3 and 4 and summarized here. They include methods for a retrospective cohort review and a cascade of care gap analysis.

4.2.1 Objectives and variables

The quantitative phase addressed the following two study objectives:

> *Objective 1:* To compare the socio-demographic characteristics between patients who are diagnosed and treated, with those who are diagnosed and untreated within the cohort of patients diagnosed with DR-TB in 2015;
>
> Objective 2: To quantify gaps along the DR-TB continuum of care cascade, and highlight areas for improvements in access to care;

The outcome and independent variables used in this phase are detailed in Table 6.

Table 6: ***Study variables***

Dependent variables	Descriptions
DR-TB incidence	Estimated number of individuals with DR-TB in the annual tuberculosis burden
Tested	Number of individuals with DR- TB who accessed TB tests proportion of DR-TB among new and previously treated patients among notified pulmonary TB cases
Diagnosed	Number of individuals with DR TB who were successfully diagnosed in the National diagnosis register
Treated	Number of individuals initiated on DR-TB treatment in the National treatment register
Completed treatment	Number of patients who complete TB therapy in the National treatment register
Treatment initiation	Dichotomous: diagnosed and treated versus diagnosed and untreated
Timely treatment	Dichotomous: treated early (time to treatment within 1 month) versus treated late (time to treatment greater than 1 month)
Patient-level independent variables	Descriptions
Sex	Female/male
Age	0-19, 20-59 and >=60
Place of residence	Rural or urban
Treatment history	New, retreatment, relapsed, default and unknown history
Type of resistance	Mono, rifampicin or multi-drug resistant

Health system-level independent variables	Descriptions
Geopolitical zone	North-East, North-Central, North-West, South-East, South-South and South-West
Treatment level	Community-based, facility-based
Type of diagnosis facility	National/zonal laboratory, Federal, State-owned or private hospital

4.2.2 Study population and data collection

The primary population for this phase included the cohort of patients diagnosed with DR-TB using GeneXpert MTB/RIF technology between January 1st and December 31st, 2015. These records were individually tracked to the treatment database to determine if initiated on treatment and when. Treatment initiation records for this cohort were tracked up to August 2017 (20-32 months after diagnosis).

The diagnosis records were found in the GxAlert system, a web-based system for GeneXpert reporting. Treatment initiation records were found in the E-TB Manager, a comprehensive web-based record of all patients placed on TB treatment.

A total of 996 diagnosis records were tracked. The sampling size, strategy and timing are shown in *Figure 10.*

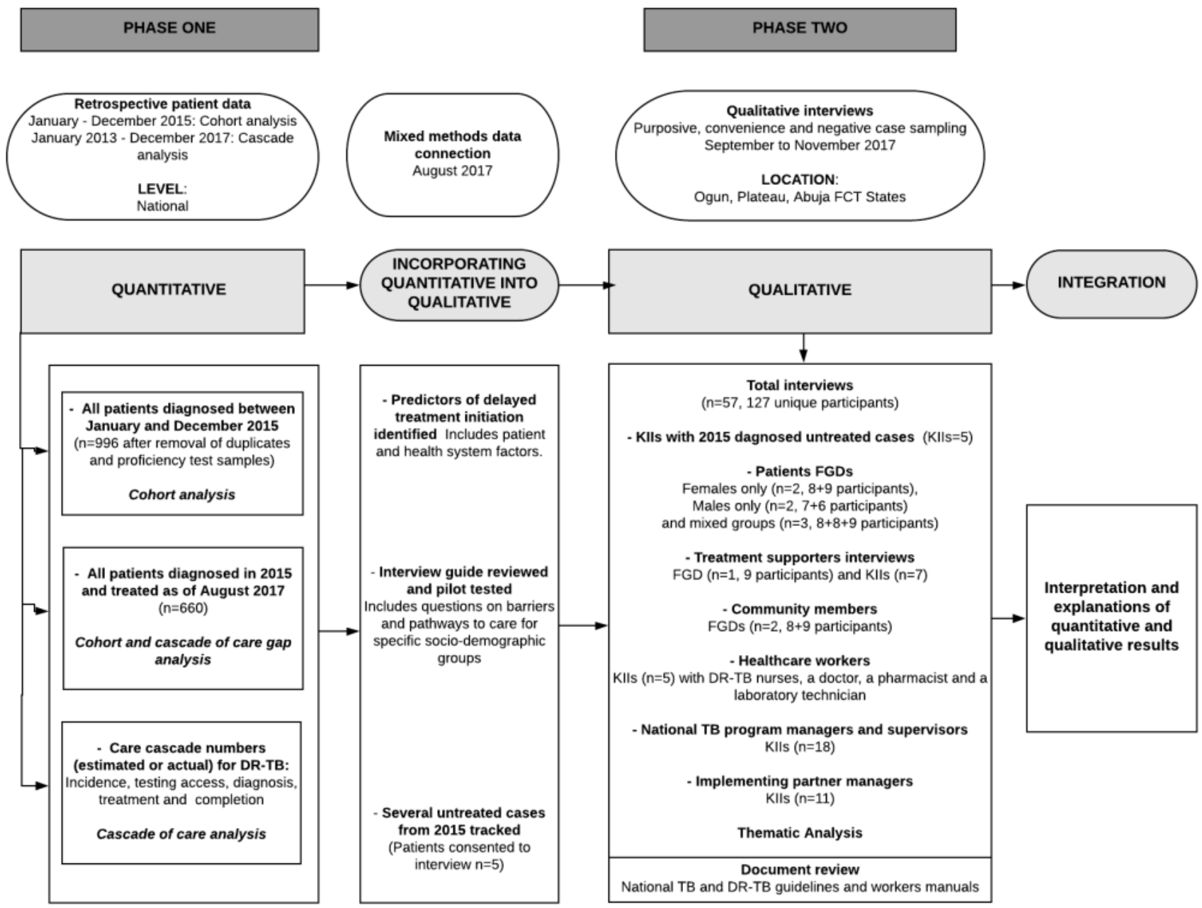


Figure 10. – Mixed methods sampling strategy

4.2.3 Data cleaning and analysis

For the cohort analysis, excel output files sourced from the GxAlert and E-TB manager were cleaned and validated before analysis. Preparation involved reducing missingness in age and sex data, using multiple imputation, and the use of names to fill in missing sex.

Data were analysed at a national level for each geopolitical zone and for states within the South-West region. We used standard descriptive statistics to characterize the cohort in both databases. We measured the association between health system and patient characteristics with the two main outcome variables - treatment initiation (untreated versus treated), and timely treatment (early versus late treatment), using binomial logistic regression while controlling for confounders. We identified predictors of treatment initiation and timeliness using multiple logistic and cox proportional hazards regressions. All statistical analysis was done using the SPSS software, version 24.

For the cascade of care gap analysis, the numbers of patients at each level of DR-TB care, including incident cases, individuals who accessed testing, were diagnosed, initiated treated and completed treatment in Nigeria between 2013 and 2017 were used to estimate losses at each stage. Using the retrospective data for patients diagnosed in 2015, we used Pearson chi-square to determine the association between patient (age and gender) and provider (geopolitical zone) variables, permitting a closer look at the gaps in care revealed across the 5 years.

Most of the statistical analysis was done using SPSS software, version 24. Other analytical procedures are detailed in articles 3 and 4.

4.2.4 Unique data linkage challenges

We used a deterministic approach to link records based on surname, first names, sex, age and address between the two registers because there were no unique patient identifiers. Deterministic records linkage methods are used to link records in databases that lack a unique identifier; it combines various identifying variables to generate a unique identification key.

A proportion of the records in both databases could not be matched. For patients found in the diagnosis register and not in the treatment register, they were classified as 'untreated' and compared with patients diagnosed and treated. Patients found in the treatment database and not in the diagnosis database were excluded in the initial cohort analysis but included for the cascade of care analysis.

Record linkage was a challenge in the absence of a unique patient identifier, and the large proportion of data with missingness.

4.3 Connecting Quantitative and Qualitative Phases

Results from the quantitative analyses above was used to inform qualitative data collection tools and analysis. Differences in treatment initiation and timeliness between socio-demographic groups were explored with document evaluation and qualitative interviews. Based on quantitative results, patients from significant socio-demographic groups and their relatives were purposefully selected for interviews. The in-depth interview and focus group discussion questions were adapted to reflect the issues specific to the identified socio-demographic groups. By adapting the qualitative research to the issues identified from the quantitative phase, we used the qualitative phase to more deeply explore the identified socio-demographic differences in healthcare access.

4.4 Methods for the qualitative phase

The full details of the qualitative methods are detailed in articles 4 and 5 and summarized here. They include qualitative data for the cascade gap analysis, and the ease and equity of access analysis using documentary review and key informant interviews and focus group discussions.

4.4.1 Embedded qualitative case study components

An embedded case study approach usually allows for more relationships to be compared and offers more opportunities for generalization (Creswell, 1998, Yin, 2013). recommends five critical sections for case study designs: the study question, the propositions, the units of analysis, the logic linking the data to the propositions, and the criteria for interpreting the findings. These relevant components for this study are presented in *Table 7*.

The embedded case study phase addressed the last two objectives of the research:

> *Objective 3*: To describe health systems policies, structures and procedures for DR-TB diagnosis and treatment and how these relate to diagnosis and treatment for different patient socio-demographic groups using an equity of access to healthcare framework;
>
> *Objective 4*: To qualitatively explore and describe reasons for socio-demographic differences

in access to DR-TB care from the perspectives of healthcare providers, patients and their treatment supporters.

Table 7: Five components of the embedded case study

	Embedded case study components	Methodology/Description
1	Specific case study questions (CSQ)	1. How do relevant DR-TB policies, structures and processes in Nigeria relate support diagnosis and treatment initiation? 2. What are the views and experiences of DR-TB health care providers on access to DR-TB treatment in Nigeria? 3. How accessible, from the perspective of DR-TB patients and their relatives in Nigeria, are DR-TB treatment services?
2	Propositions	CSQ 1: *Policies, Structures and Processes for DR-TB Treatment Initiation* 1. DR-TB-specific policies are available to direct the Nigeria's national response 2. Nigerian DR-TB policies have not given adequate attention to available access options for certain socio-demographic groups 3. The number of service points and personnel to diagnose and treat DR-TB are inadequate based on estimated number of patients in need 4. The process for diagnosis and initiating treatment for DR-TB contains barriers to certain socio-demographic groups of patients 5. The provision of DR-TB services is limited to the public sector. 6. There is inadequate private sector engagement and referral system for case finding 7. DR-TB services in Nigeria are mostly funded by donor funds, threatening sustainability CSQ 2: *Views and experiences of DR-TB health care providers* 1. Providers believe that available inputs (funding, facilities, products) for diagnosing and treating DR-TB are inadequate (*availability*) 2. Providers encounter structural and patient-level challenges in providing DR-TB services 3. Providers believe DR-TB services are sufficiently *approachable* for DR-TB patients 4. Providers believe DR-TB services are sufficiently *acceptable* for DR-TB patients 5. Providers believe DR-TB services are sufficiently *affordable* for DR-TB patients 6. Providers believe DR-TB services are sufficiently *appropriate* for DR-TB patients CSQ 3: *Perspective of DR-TB patients and their treatment supporters* 1. Certain DR-TB patients travel long distances (more than 2 hours) to access diagnostic and treatment services 2. The multiple clinic visits required for diagnosis and treatment initiation are inconvenient for patients 3. Rural patients face more difficulties in accessing diagnosis and treatment 4. Female patients face more difficulties in accessing diagnosis and treatment 5. Children patients face more difficulties in accessing diagnosis and treatment 6. Married patients face more difficulties in accessing diagnosis and treatment 7. Low income (informal sector or unemployed) patients face more difficulties in accessing diagnosis and treatment 8. The treatment related out-of-pocket costs for DR-TB are prohibitive for patients 9. The burdens of accessing diagnosis and treatment for DR-TB is disproportionately borne by certain socio-demographic groups of patients
3	Units of analysis	1. Relevant DR-TB-specific policies, structures and processes in Nigeria and how they relate to DR-TB treatment initiation.

		Data from interviews will be supported by reviewing documents from the DR-TB policy makers: the Federal Ministry of Health (MOH), and the National TB and Leprosy Control Program (NTBLCP). Comparisons between documents and interview data will be made. 2. Views and experiences of DR-TB care providers In-depth interviews will be conducted with clinic and community DR-TB personnel in Ogun state, Nigeria. Cross-case comparisons will be made between data from healthcare providers at the state level with those within the communities. 3. Perspective of patients on DR-TB diagnosis and treatment accessibility (availability, acceptability, affordability): Participants will be selected for in-depth interviews from specific socio-demographic groups in Ogun state as identified by the quantitative data.
4	Logic linking data to propositions	Pattern-matching procedure of data analysis will be used. The analysis is aimed at exploring the factors that relate to DR-TB treatment initiation in Nigeria using the conceptual framework as a basis. A proposition will be made for each concept in the framework and used in the study questionnaire.
5	Criteria for interpreting results	The analysis will compare the respondents' responses to each question, linking back to the *a priori* propositions. Cross-case comparisons will also be done

4.4.2 Study population and data collection

We conducted qualitative interviews of patients who were currently on treatment, their relatives and providers in Ogun and Plateau States, as well as program managers in Benue and Abuja, the Federal Capital Territory (FCT) between August and November 2017. A total of 57 interviews were conducted in these States, including 10 focus group discussions (FGDs) and 47 key informant interviews (KIIs). The total number of distinct study participants was 127. No participants were interviewed more than once (KII plus FGD). The sampling strategy is shown in *Figure 10*.

Our main sampling strategy was purposive, selecting participants whose views would most likely be information-rich about delays in DR-TB care and to enhance study credibility. The data collection process interrogated ways in which a patient's sociodemographic characteristic affected their pathway to care- particularly sex, gender, geographical location, and income. We used maximum variability to select participants based on sex, position or role in the TB care system (patients including treated and untreated, relatives including parents, community members, health worker or manager), and geographical location, to reflect these different sociodemographic groups. Interview guides with all groups of participants repeatedly questioned and probed participant's perspectives on how a patient's characteristic might affect their access to care.

Our aim was to understand these barriers from the perspectives of users and providers, as well as their treatment supporters and program managers. Within this sampling approach, we selected participants based on availability and consent. We also used extreme or negative cases to provide additional insight into barriers to treatment initiation. In some cases, this sampling method can offer the purest form of insight into the phenomenon being studied (Moser and Korstjens, 2018).

Healthcare worker questions addressed DR-TB program structure, challenges and strengths, as well as their perception of access barriers and facilitators. Patients, treatment supporters and community members were also asked to describe barriers and facilitators to accessing DR-TB care that they, their relative or someone they knew had experienced. Female and male only groups were additionally probed for any particular challenges facing their gender in accessing care. Community member FGDs probed community beliefs and practices around TB. The phone interviews were done with cases diagnosed in 2015 that could not be traced in the treatment registers to contrast with patients who were already on treatment.

In addition to the questions for healthcare workers, program managers and implementing partner interviews were asked about the available resources at the national, regional and state level for DR-TB care, their perspectives on the adequacy of these resources, and relevant policy documents on DR-TB care. The recommended documents and guides were also analysed using our adapted equity of healthcare access framework.

Patients and healthcare workers in two of the bigger treatment centers in the Southwest and North Central geopolitical zones- the Sacred Heart Hospital, Abeokuta, which has the largest number of bed spaces (48) for treating DR-TB patients in Nigeria; and Jos University teaching hospital teaching hospital with 34 bed spaces for DR-TB treatment. Community interviews were also conducted in communities surrounding these two centers.

Initial interview guides were developed by the doctoral researcher, with inputs from the thesis supervisors before data collection, after an initial review of literature. The interview guides and sampling strategy were reviewed and adjusted based on an initial rapid quantitative analysis to identify socio-demographic groups with increased risks of poor access to care. The interview guide was piloted at the beginning of the data collection. The informed consent forms and interview guides are included in the appendix 1.

We conducted initial entry meetings with National and State TB program coordinators, as well as clinic managers at both treatment centers to discuss the overall objectives of the research and sampling strategies.

Informed consents from each participant were written or verbally acknowledged before each interview. The doctoral researcher with the field assistant conducted the interviews. Interviews with patients were conducted outdoors in the treatment centers, and with patients who have been on treatment for more than two weeks. Interviews were conducted in English and respondents were encouraged to respond in or ask for translation into Nigerian pidgin, Yoruba or Hausa as needed, which were the predominant languages spoken in those regions. There were some instances of translation from the Yoruba language, and pidgin English by the research assistant, who is fluent in both languages and English, and was trained in qualitative research. Translations were double-checked with a native speaker. Interviews were audio-recorded.

Transcription of audio recordings were outsourced after a confidentiality agreement. Transcripts were sent back to all participants who had earlier agreed to be contacted for accuracy checking, some of who responded with revised transcripts which were used to replace the original transcripts.

4.4.3 Qualitative data analysis

Data analysis began during data collection to enable exploration and comparisons of new themes. We used inductive and deductive approaches. Our literature review and interview guide were used to deductively develop a coding tree before the process of coding began. Transcripts were checked and read through to give a general understanding of the data. Coding was inductive to allow new themes to be added to the coding tree. Codes were matched to the coding tree or assigned new codes. Coding of documents and interview transcripts were around themes based on our conceptual framework of Equity of access to DR-TB care discussed in chapter 2. The thematic analysis focused on how the system facilitates patient progression after arrival with symptoms at the TB clinic to the point of treatment initiation, as well as on patient pathways to care. This is aimed at providing a better understanding of the quantitative data. A summary of the coding tree is attached in appendix 2.

Document analysis helped to triangulate evidence from the in-depth interviews. This also facilitated member checks (participant feedback on emerging themes) to ensure fidelity with participant intents as recommended by Seale (Seale, 1999). An iterative and reflexive data collection, combined with member checking, facilitated a better understanding of themes and enabled better strategies for continuing data collection to fill existing gaps in the data. Data analysis was facilitated by the use of the Quirkos software, version 1.6.1. Our findings were reported using the consolidated criteria for reporting qualitative studies (COREQ) (Tong et al., 2007).

The same qualitative data were analysed concurrently for the different research questions (Objectives 3 and 4), and the analyses are reported in two separate papers (Article 4 and 5). Most, if not all, quotes were representative of the main themes identified either from multiple sources across different hospitals or were quotes from FGDs where most of the participants showed assent. We selected representative quotes based on either the richness of the descriptions or the range of issues mentioned by one speaker.

4.5 Integration of the Quantitative and Qualitative Results

To integrate results from both phases, the final step in the study summarized the results, and our interpretation of the results were done in the light of both the quantitative and qualitative findings. More specifically, an initial cohort analysis was used to revise the qualitative interview guide and participant selection. The results of the cohort analysis were published separately in Article 3. The preliminary qualitative analysis prompted a cascade analysis, to further explore how dropouts from the care system were related to patients' socio-demographic characteristics. The cascade analysis is presented in Article 4, which is a mixed methods paper. In article 5, we present additional perspectives from the qualitative results, to highlight the equity of DR-TB policies, structures and processes.

4.6 Ethics considerations

At the beginning of the research process, ethical approval was sought and obtained from two ethical review boards: National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007); and from the Research Ethics Committee of the University of Montreal Hospital (CER 17.060). An additional ethical approval was obtained from the Research Ethics Committee (CER) of sciences and health of the University of Montreal (CERSES-19-098-D). All participants gave written informed consent. All certificates of ethics approval, participant information sheet and informed consent form are provided are attached in appendix 3.

Other ethical considerations involved ensuring participant anonymity by using a numeric code for each interview, keeping research files password-protected in a laptop and physical files kept in a location only accessible to the first author. The physical files and will be kept for up to a period of 10 years, after which they will be destroyed. In order to further protect the participants, the interview language was kept simple, and the interviewers were reflexive and used active listening. Participants information sheets, which were also read out and interpreted where necessary, contained contact information for a local counselor, should their services be needed.

In the process of data collection, untreated patients were flagged with the TB control officers. In one of the cases, an adult patient's male relatives indicated that they wanted no contact from the DR-TB program. As this was without her consent, we flagged her information as well.

In order to minimize the risk of infection to the doctoral researcher and research assistant, only patients who had been on treatment for longer than a month (and no longer infectious), were interviewed. As an extra precaution, all patient interviews took place outdoors.

CHAPTER 5: RESULTS

Overview of results chapter

I used a sequential transformative mixed methods approach to explore the problem of low diagnosis and treatment coverage in Nigeria. The results of this study are presented in 3 articles, each in response to specific research questions and objectives, as identified in Chapter 1. To recap:

The research questions are:

4. What are the health system and patient factors that influence diagnosis and treatment for DR-TB in Nigeria?
5. What are the percentage dropouts and factors associated with attrition between each stage of the DR-TB care cascade?
6. Do the policies, structures and procedures for DR-TB support the diagnosis and treatment in Nigeria for different patient socio-demographic groups?

The research objectives are:

1. To compare the socio-demographic characteristics between patients who are diagnosed and treated, with those who are diagnosed and untreated within the cohort of patients diagnosed with DR-TB in 2015;
2. To quantify gaps along the DR-TB continuum of care cascade, and highlight areas for improvements in access to care;
3. To qualitatively explore and describe reasons for socio-demographic differences in access to DR-TB care from the perspectives of healthcare providers, patients and their treatment supporters.
4. To describe health systems policies, structures and procedures for DR-TB diagnosis and treatment and how these relate to diagnosis and treatment for different patient socio-demographic groups using an equity of access to healthcare framework.

The first article (Article 3) is a retrospective cohort study of DR-TB diagnosis and treatment database for patients diagnosed in 2015. It aimed to explore health system and patient factors associated with initiation and timeliness of treatment among DR-TB patients in Nigeria. This article targets the first research question and the first objective. It was published in PlosOne Journal (April 2019).

The second article (Article 4) is a mixed methods cascade analysis of DR-TB care in Nigeria. The study described the Nigerian DR-TB care cascade from 2013-2017 and considered factors influencing gaps in care. The article answers the second research question, as well as the second and third objective. It has been submitted to the Journal of Clinical Tuberculosis and Other Mycobacterial Diseases in July 2020.

The third article (Article 5) presents results from a qualitative analysis of policies, structures and processes. It analyzed the ease and equity of access to free DR-TB services in Nigeria, by exploring elements that facilitate or hinder equitable access for different groups of patients within the current health system to support DR-TB management in Nigeria. This article, which focused on the third research question and fourth objective, was submitted to the International Journal for Equity in Health (July 2020).

Article 3: Cohort study

Title page

Title: Rates and Timeliness of Treatment Initiation among Drug-Resistant Tuberculosis Patients in Nigeria- A Retrospective Cohort Study

Authors and affiliations:

Charity Oga-Omenka [1,2], Christina Zarowsky[1,2], Aderonke Agbaje[3], Joseph Kuye[4], Dick Menzies[5],

1. School of Public Health of the University of Montreal (ESPUM), Canada
2. Public Health Research Institute of the University of Montreal,(IRSPUM), Canada
3. Institute of Human Virology Nigeria
4. National TB and Leprosy Control Program, Federal Ministry of Health, Nigeria
5. McGill University International TB Centre, Montreal, Quebec, Canada

Corresponding author:

Charity Oga-Omenka

Acknowledgements:

The authors thank the National TB and Leprosy Control Program (NTBLCP) of the Federal Ministry of Health (in Abuja and Ogun State), the International Research Center for Excellence (IRCE) of the Institute of Human Virology Nigeria (IHVN) for granting access to the National database for support in the process of data collection.

The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the Global Fund, NTBLCP or IHVN.

Status: This article was published in the PlosOne journal in April 2019

https://doi.org/10.1371/journal.pone.0215542

Abstract:

Background:

There were an estimated 580,000 new cases of multidrug/rifampicin resistant TB (DR-TB) in 2015, and only 20% were initiated on treatment. This study explored health system and patient factors associated with initiation and timeliness of treatment among DR-TB patients in Nigeria, ranked 4th globally for estimated TB cases in 2015.

Methods:

A retrospective cohort study using 2015 diagnosis and treatment data from the Nigerian TB program electronic records examined "treatment ever received" (yes/no) and "treatment within 30 days" (yes/no). We compared health system and patient characteristics using binomial logistic regression, while controlling for confounders.

Results:

Of 996 patients diagnosed nationwide in 2015 (aged 0-87 years, median 34), 47.8% were never treated. Of those treated (n=520), 51.2% were treated within the 30 days prescribed in the National treatment guideline. Healthcare facility locations were significantly associated with ever receiving treatment and timely treatment. Predictors of timely treatment at the national level also included level of care and patient treatment history. The South-West zone, where DR-TB programs started, showed overall better access to DR-TB healthcare.

Conclusions:

Healthcare facility geographic locations were significantly associated with treatment initiation and timeliness. Significant regional differences in access to DR-TB care in Nigeria persist, reflecting uneven contexts for national DR-TB treatment rollout.

Key words (max 5): rifampicin-resistant; tuberculosis; time to treatment; health systems; Nigeria

Introduction

There were an estimated 10.4 million incident TB cases worldwide in 2015 (25% in Africa) and 580,000 DR-TB new cases (WHO, 2016a). Although DR-TB survival rates are lower and treatment more difficult, studies have suggested that treatment outcomes are optimized by timely diagnosis and treatment, as mortality rate is highest within the first month of diagnosis (Turett et al., 1995, Gandhi et al., 2010b, Pablos-Méndez et al., 1996). The World Health Organization (WHO) recommends treatment initiation within 4 weeks of diagnosis (Falzon et al., 2017).

In 2015, only 20% of new DR-TB cases were initiated n treatment (WHO, 2016a). Five countries, including Nigeria, made up more than 60% of this gap in treatment (WHO, 2016a). Nigeria, ranked 4th globally for estimated TB cases (586,000 incident cases and 29,000 new DR-TB cases), is one of 14 countries categorized by the WHO as having overlapping high burdens of TB, DR-TB and HIV (WHO, 2016a, WHO, 2018b). Of these, however, only 90,584 TB and 1,241 drug resistant incident cases were notified in 2015, giving a case detection rate (CDR) of 15% and 4.2% respectively, some of the lowest globally (WHO, 2016a). These low rates highlight major difficulties in accessing TB diagnosis and treatment.

Nigeria commenced free DR-TB treatment in 2010 with a hospital-based care model and adopted the use of Xpert MTB/RIF technology in 2011, leading to an increase in case detection (Gidado et al., 2014, Tope et al., 2014). Community DR-TB treatment initiation commenced in 2013 and was scaled-up in 2015.(NTBLCP, 2014) Available literature does not clearly document how long DR-TB patients are waiting to be started on treatment, nor the socio-demographic differences between diagnosed and untreated patients and those who are treated.

We conducted a retrospective review of national diagnosis and treatment electronic medical records (EMR) between January to December 2015 in order to estimate the proportion and characteristics of patients not started on treatment within one month after diagnosis.

Materials and methods

Study Setting

Nigeria, the most populous country in Africa with an estimated population of 183 million people in 2015 (NBS, 2016a), has 37 States divided into 6 geopolitical zones: North-Central, North-East, North-West, South-East, South-South and South-West (*figure 11*). Since 2011, the Federal Ministry of Health has implemented DR-TB care, with support from the Global Fund and other partners(FMOH, 2012a)(FMOH, 2012a)(FMOH, 2012a)(FMOH, 2012a)(FMOH, 2012a)(FMOH, 2012a)(FMOH, 2012a) in 28 tertiary and secondary facilities within 27 States (FMOH, 2012b, Gidado et al., 2018).

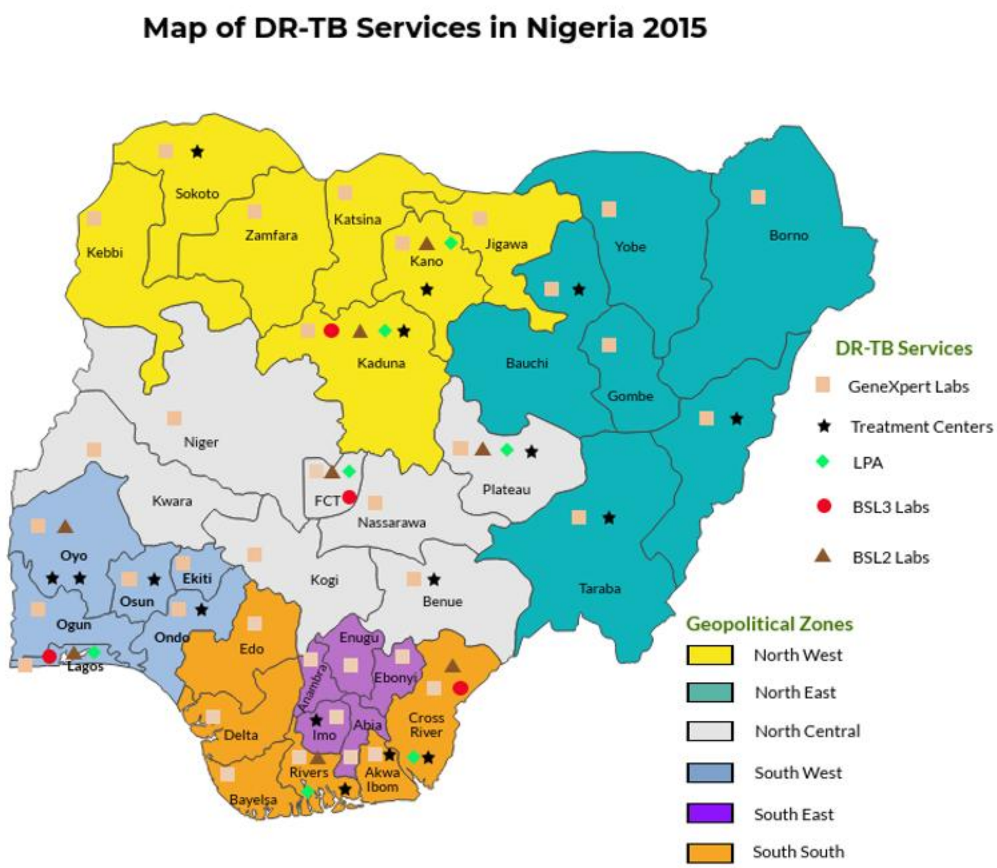


Figure 11. – Map of Nigeria showing coverage of DR-TB Services as at November 2015

The national treatment guidelines recommend that patients be placed on treatment within one month of diagnosis (WHO, 2016a, Turett et al., 1995). A web-based system for GeneXpert reporting, the GxAlert, was introduced in 2012 which facilitates the flow of patients, samples, and results at facility level by transmitting instant SMS results to clinicians and patients (NTBLCP, 2015a, Mustapha et al., 2015).

By the end of 2015, the National TB and leprosy control program (NTBLCP), reported 201 GeneXpert sites (Otu, 2013) and a total of 52,219 GeneXpert tests performed using 176 machines. Of these, 11,745 (22.5%) were positive for Mycobacterium tuberculosis, with 1,264 Rif-resistant (Mustapha et al., 2015).

Similar to the DOTS strategy before it, treatment for DR-TB in Nigeria began in the SW zone in 2010 before being scaled to other regions. The SW region had the only national reference laboratory for several years; and at the end of 2015, had the highest numbers of gene expert machines installed, patients diagnosed, hospital beds and patients enrolled for DR-TB treatment (NTBLCP, 2015a, Otu, 2013, NTBLCP, 2014). The National TB prevalence survey showed that the SW zone had the highest incident cases of TB,(NTBLCP, 2012) and several studies have indicated that the zone also has the highest incidence of DR-TB (Otu, 2013, Gehre et al., 2016, Onyedum et al., 2017).

Definitions

Time to treatment initiation (TTI) was defined as the interval between the dates of diagnosis of DR-TB and the initiation of anti-TB treatment. “Untreated” was defined as patients diagnosed in 2015 who had not started treatment by the end of August 2017. “Treated” patients were further categorised into “Early” if initiated between 0-30 days and “Late” if more than 30 days.

Two types of DR-TB facilities- diagnosis and treatment - were further categorized. Types of diagnosis facility included “Reference laboratories” (2 national and 6 zonal reference laboratories), “Federal hospital” (tertiary facilities), “State-owned” (secondary facilities), “Primary Hospital” (Primary health care administered by the local government areas (LGA)) and “Private Hospital”.19 Levels of treatment facilities included “Facility-based” (for patients who started DR-TB treatment as in-patients) and “Community-based” (for those who started treatment as out-patients).

The geographical size classification was based on the 2015 estimated population of each LGA in Nigeria (NBS, 2016a, NBS, 2016b). LGAs with more than 400,000 were classified as “Urban”, between 250,000 and 400,000 as “Semi-Urban” and less than 250,000 as “Rural”.

Case detection rate, patient treatment history and type of resistance were classified based on the WHO and national DR-TB definitions.(WHO, 2006, WHO, 2013, NTBLCP, 2008)

Study Design

A retrospective cohort was identified of diagnosed DR-TB patients in 2015 from the Nigerian National TB program EMR. Patients were tracked by checking treatment initiation records up to August 2017 (20-32 months after diagnosis).

The first data source for this study was the GxAlert data, which included patients diagnosed with Mycobacterium tuberculosis (MTB) and resistance to rifampicin (RIF) using GeneXpert MTB/RIF technology in 2015.

The second data source, the e-TB Manager is a comprehensive web-based record of all patients placed on TB treatment.

All valid entries for diagnosed patients who were diagnosed (GxAlert database) and treated (e-TB Manager Database) in 2015 were analyzed to estimate treatment waiting times and to identify socio-demographic differences between treated and untreated patients among the diagnosed populations.

Data linkage process

We used a deterministic approach for records linkage based on surname, first names, sex, age and address from the different registers because they did not contain unique patient identifiers. As shown in Figure 12, among the 996 cases of TB diagnosed and registered in the Diagnosis (GXAlert) database in 2015, 52.2% (n=520) were also registered in the treatment (e-TB Manager) database and were matched.

A proportion of the records in both databases could not be matched. For patients found in the diagnosis register and not in the treatment register (n=476), they were classified as 'untreated' and compared with patients diagnosed and treated. Patients found in the treatment database and not in the diagnosis database were excluded (n=140), with a description of their basic characteristics presented in *Table 8*.

Statistical Analysis

Diagnosis and treatment data were analysed at the national and at the SW regional levels. Excel data files sourced from the GxAlert and E-TB manager were cleaned and validated before analysis. Data preparation involved matching sex to names (missingness reduced from 10.0% to 3.3%) and the use of multiple imputation to handle missing data, specifically for age (missingness reduced from 21.7% to 0.3%) and sex (from 3.3% to 0.0%), after a determination of missing completely at random (using the Little's MCAR test). Missing values were imputed using the automatic settings of the multiple imputation method and random number generator (Mersenne Twister). A total of 10 data sets of imputed values were created and used in subsequent analyses for both databases, and pooled results reported. Standard descriptive statistics were used to characterize the cohort in both databases. We measured the variance inflation factor (VIF) in the variables in order to detect and exclude the existence of collinearity, and subsequently logistic regression analyses. Univariate binary logistic regressions were used to estimate crude odds ratios and their 95% confidence intervals (CI) for the association between socio-demographic differences (age, sex, type of facility, geopolitical regions) and two outcome variables - treatment initiation (untreated versus treated), and timely treatment (early versus late treatment) among those diagnosed in 2015. Multiple logistic regression models were used to identify predictors of treatment initiation and its timeliness. Cox proportional hazards regression was used to simultaneously assess the effect of several socio-demographic factors on TTI, where survival time was the TTI in days. Patients were censored when not placed on treatment as at August 2017 (≥601 days) Statistical significance for all analysis was pegged at 5% level (0.05). Violation of proportional hazard assumptions was checked by examining the Log−log plots with the aim of excluding any covariates which violated the assumptions. All statistical analysis was done using the SPSS software, version 24.

Ethics Statement

Ethical approval was obtained from the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007). Approval was also received from the Research Ethics Committee (CER) of the University of Montreal Hospital (17.060).

Results

Characteristics of DR-TB patients

From January to December 2015, a total of 996 entries out of 1264 unique diagnosis entries were selected for analysis, after duplicates and routine proficiency tests were excluded. Diagnosed patients' records were matched with treatment records using patient name, sex, age and address, as well as the test and treatment dates, as the two databases were not linked using unique patient identifiers. Out of 996 diagnosed patients, 52.2% (n=520) were found to have been placed on treatment, out of which 2 patients were excluded because their treatment start dates were not found. Of the 518 patients with treatment start dates, 51.2% (n=265) were placed on treatment early; of the 253 placed on treatment late, 26.6% were between 31 and 60 days, 19.3% between 61-180 days and 2.9% >180 days. *Figure 12* shows how study participants were selected and included.

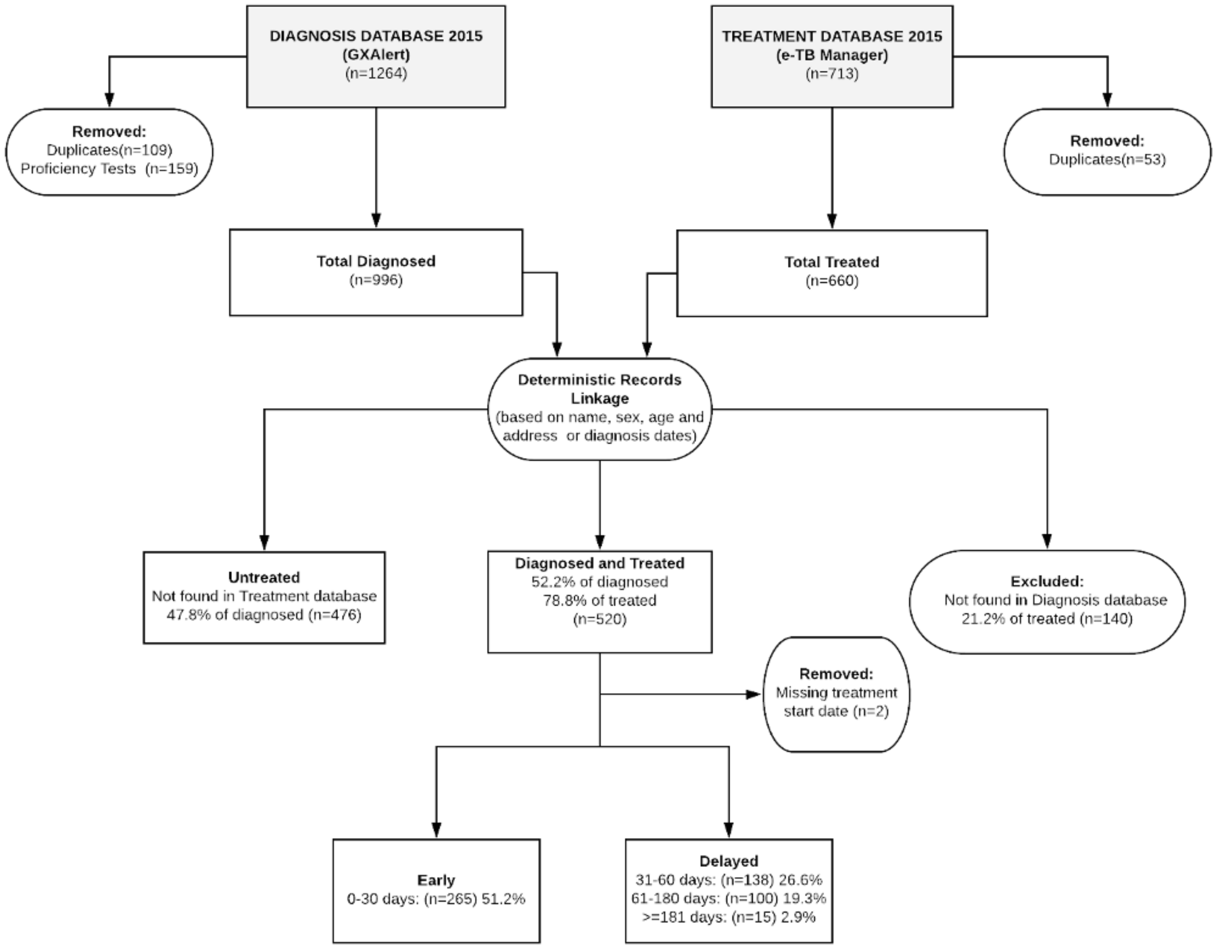


Figure 12. – Flow diagram of study recruitment strategy

Demographic statistics and outcomes for study participants are summarized in *Table 8*. The median age for the study population was 34.0, with males comprising 65.0%. Over half of the patients came from the South West and North Central regions, with 28.7% and 25.1% respectively, and were diagnosed or treated in an urban facility (52.8%). More patients were diagnosed in higher level facilities (State-owned= 39.9%; Reference lab=31.7% and Federal Hospital = 21.4%) than in the primary care centers or private hospitals (1.6% and 5.4% respectively).

Some 2015 treatment enrolled patients (n=140 and representing 21.2% of total treatment initiations) found in the treatment database could not be traced in the diagnosis (GxAlert) database and were excluded. Their characteristics are also included in *Table 8*. The median age was 37.0 and 77.1% were male. Most of the patients were from the South West (37.9%) and North West (25.7).

Table 8: Description of basic characteristics of study and excluded population

Table 8: *Description of basic characteristics of study and excluded population*		
Characteristic	Study Population	Excluded*
TOTAL	*996*	*140*
	n (%)	*n (%)*
Age		
Children (0-19)	80 (8.0)	5 (3.6)
Adults (20-59)	870 (87.3)	125 (89.3)
Seniors (≥60)	43 (4.3)	10 (7.1)
Missing	*3 (0.3)*	*0*
Range	0 – 87	15 – 77
Mean (SD)	35.45 (12.79)	38.37 (12.11)
Median	34.00	37.00
Sex		
Female	349 (35.0)	32 (22.9)
Male	647 (65.0)	108 (77.1)
Geopolitical Region		
South West	286 (28.7)	53 (37.9)
North Central	250 (25.1)	18 (12.9)
South South	143 (14.4)	21 (15.0)
North West	116 (11.6)	36 (25.7)
South East	107 (10.7)	9 (6.4)
North East	94 (9.4)	3 (2.1)

Urban/Rural		
Urban	526 (52.8)	83 (59.3)
Semi-Urban	290 (29.1)	33 (23.6)
Rural	180 (18.1)	21 (15.0)
Missing	-	4 (2.1)
Type of Diagnosis Facility**		
National/Zonal Laboratory	316 (31.7)	-
Federal Hospital	213 (21.4)	-
State-owned Hospital	397 (39.9)	-
Primary Hospital	16 (1.6)	-
Private Hospital	54 (5.4)	-

* These 140 patients were registered in the treatment database (e-TB manager) as diagnosed in 2015 but could not be traced in the diagnosis database (GxAlert).

** The treatment database, where the 140 patients were found, did not have information about the type of diagnosis facility

Treatment Initiation: Characteristics and Predictors

At the national level, treatment initiation did not vary significantly between socio-demographic groups, although there were significant predictors at the geopolitical level. Among the 6 categorical variables tested, none had statistically significant associations with treatment initiation. However, logistic regression showed patients diagnosed in the South East (SE) and North East (NE) were less likely to be initiated on treatment compared to their counterparts in the South West (SW) (AOR: 0.57, 0.35-0.93 and 0.61, 0.37-1.00) respectively. *Table 9* compares treatment initiation outcome for different socio-demographic groups and between different types of diagnostic facilities.

Further analysis in the SW zone showed similar locational differences, comparing treatment initiation differences between states in the region and for different socio-demographic groups. Among the 5 categorical variables tested, only the state within which patients were diagnosed showed statistical significance with treatment initiation. However, in adjusted logistic regression models, adults (ages 20-59) were less likely (AOR: 0.30, 0.10-0.96) than children (0-19) to be initiated on treatment. Also, Ogun State patients (as reference group) were also more likely to be initiated than the other states in this region. Patients in Ekiti and Ondo States were less likely (AOR: 0.08, 0.01-0.93 and 0.02, 0.002-0.15) to be initiated.

Comparing the likelihood of treatment initiation and the time-to-event was done using the Cox proportional hazard model, and was adjusted for age, sex, urban/rural and geopolitical zones (figure 13), as an examination of the log minus log plots did not show any of these covariates as violating the assumptions. In the Cox Proportional Hazard modeling time to treatment, patients in the NE were less likely to be

__Table 9: National and regional characteristics and predictors of treatment initiation__

Individual and Community Level Characteristics	National level					SW Region only				
	Treatment initiated*			Predictors		Treatment initiated*			Predictors	
	N	Yes n(%)	No %	Crude OR (95% CI)	AOR** (95% CI)	N	Yes n(%)	No %	Crude OR (95% CI)	AOR** (95% CI)
Sex										
Female	349	184 (52.7)	165 (47.3)	1.0 (reference)	-	105	59 (56.2)	46 (43.8)	1.0 (reference)	-
Male	647	336 (51.9)	311 (48.1)	0.97 (0.73-1.26)		181	101 (55.8)	80 (44.1)	0.98 (0.61-1.60)	-
Age Groups										
Age as a continuous variable	80	46 (57.5)	34 (42.5)	1.00 (0.99-1.02)	1.00 (0.99-1.02)				0.99 (0.98-1.01)	
Children (0-19)	870	450 (51.7)	420 (48.3)	1.0 (reference)	-	24	17 (70.8)	7 (29.2)	1.0 (reference)	-
Adults (20-59)	43	24 (55.8)	19 (44.2)	0.79 (0.50-1.26)	0.79 (0.50-1.26)	254	138 (54.3)	116 (45.7)	0.49 (0.20-1.22)	0.30 (0.10-0.96)
Seniors (≥60)	80	46 (57.5)	34 (42.5)	0.93 (0.44-1.97)	0.93 (0.44-1.97)	8	5 (62.5)	3 (37.5)	0.69 (0.13-3.68)	0.32 (0.05-2.18)
Type of Diagnosis Facility										
National/Zonal Laboratory	316	172 (54.4)	144 (45.6)	1.0 (reference)		115	68 (59.1)	47 (40.9)	1.0 (reference)	
Federal Hospital	213	111 (52.1)	102 (47.9)	0.88 (0.65-1.18)		68	40 (58.8)	28 (41.2)	0.99 (0.54-1.82)	

State-owned Hospital	397	203 (51.1)	194 (48.9)	0.84 (0.31-2.29)		100	51 (51.0)	49 (49.0)	0.72 (0.42-1.24)	
Private Hospital	16	8 (50.0)	8 50.0)	0.78 (0.44-1.39)		3	1 (33.3)	2 (66.7)	0.35 (0.03-3.92)	
Urban/Rural†										
Urban	526	274 (52.1)	252 (47.9)	1.0 (reference)	-					
Semi-Urban	290	153 (52.8)	137 (47.2)	1.03 (0.77-1.37)	1.21 (0.89-1.66)					
Rural	180	93 (51.7)	87 (48.3)	0.98 (0.70-1.38)	1.25 (0.86-1.81)					
Geopolitical zone										
South West	286	160 (55.9)	126 (44.1)	1.0 (reference)						
North Central	250	128 (51.2)	122 (48.8)	0.83 (0.59-1.16)	0.82 (0.58-1.17)					
South South	143	75 (52.4)	68 (47.6)	0.87 (0.58-1.30)	0.88 (0.58-1.32)					
North West	116	67 (57.8)	49 (42.2)	1.08 (0.70-1.67)	1.06 (0.68-1.65)					
South East	107	48 (44.9)	59 (55.1)	0.64 (0.41-1.00)	0.57 (0.35-0.93)					
North East	94	42 (44.7)	52 (55.3)	0.64 (0.40-1.02)	0.61 (0.37-1.00)					
States (SW region)										
Ogun						36	27 (75.0)	9 (25.0)	1.0 (reference)	

Ekiti		4	1 (25.0)	3 (75.0)	0.11 (0.01-1.20)	0.08 (0.01-0.93)
Lagos		156	92 (59.0)	64 (41.0)	0.48 (0.21-1.09)	0.41 (0.18-0.96)
Ondo		14	1 (7.1)	13 (92.9)	0.03 (0.003-0.22)	0.02 (0.002-0.15)
Osun		19	10 (52.6)	9 (47.4)	0.31 (0.10-0.93)	0.26 (0.08-0.83)
Oyo		57	29 (50.9)	28 (49.1)	0.35 (0.14-0.86)	0.30 (0.12-0.76)

[a] = Continuity Correction and Phi Coefficient

[b] = Pearson Chi-Square and Cramer's V

* 'Treatment initiated' refers to whether patients diagnosed between January to December 2015 had been initiated on treatment as at August 2017

** Adjusted Odds Ratios (AOR) were obtained by comparing the likelihood of treatment initiation and the time-to-event using the Cox proportional hazard model, adjusted for age, sex, urban/rural or States, or geopolitical zones

† Some correlation was observed between the 'Urb_Rur' and 'States' variables during the test for collinearity, and the Urb_Rur was eliminated in order to build a stronger model

SW=South-West, n=number, OR= Odds Ratio, AOR= Adjusted Odds Ratio, CI=Confidence Interval treatment initiated (HR: 0.49, 0.34-0.72). Only the geopolitical zone was predictive of longer times to treatment in the adjusted model.

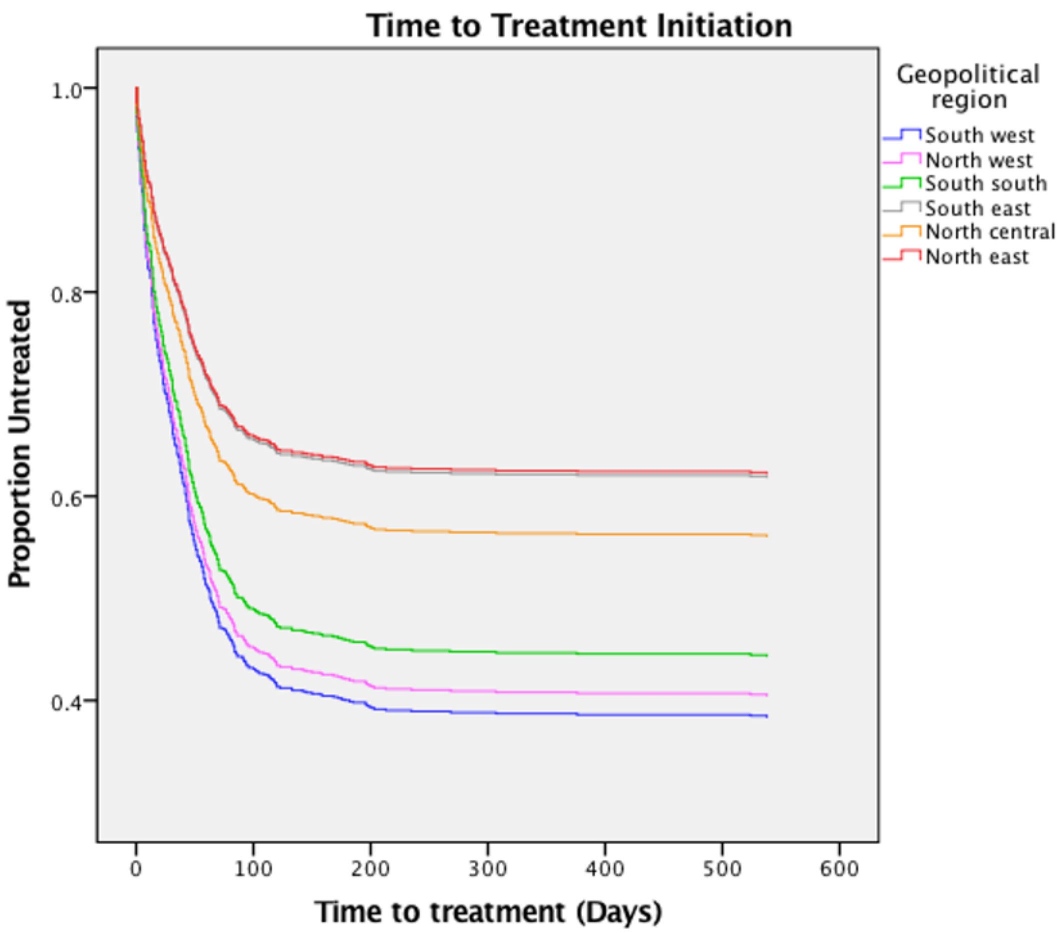


Figure 13. – Time-to-treatment initiation in the Geopolitical zones, adjusted

Timely Treatment: Characteristics and Predictors

Geographical location (semi-urban, Ogun state), level of treatment initiation (facility-/community-based), and treatment history were significantly associated with timely treatment rates across different socio-demographic groups at the National level *(Table 10).*

Patients living in semi-urban areas and patients initiating as in-patients in a hospital were more likely to experience timely initiation of treatment than those in urban areas or as outpatients (AOR: 2.11, 1.34-3.32, 1.77, 1.20-2.61).

In the SW zone (*Table 10),* State of residence, treatment initiation level (facility or community), and treatment history were significantly associated with timely treatment, much like the national level data. Ogun state residence, treatment initiation in a treatment center, and treatment-naivety were predictive of earlier treatment initiation.

Discussion

The WHO recommends early treatment initiation within 4 weeks of DR-TB diagnosis (Falzon et al., 2017) and this is prescribed the Nigerian DR-TB treatment guidelines (van de Water et al., 2017). Timely diagnosis and treatment initiation is critical for the control of DR-TB in Nigeria, one of the major contributors to the global burden of DR-TB. Our review of current literature did not find any study on the timeliness of or time to DR-TB treatment in Nigeria.

This study investigated predictors for treatment initiation and timely treatment among DR-TB patients diagnosed in 2015 in Nigeria. On average, only 3.46% of estimated DR-TB patients in Nigeria were diagnosed, only half of these were treated at all and only 1 in 4 of these received treatment within the 30 days after diagnosis as recommended by the Nigerian NTP and WHO. Our findings highlight the need to improve the timeliness of DR-TB treatment for patients in Nigeria in order that efforts to improve case detection not result in large numbers of diagnosed but untreated patients.

Geographical location of the DR-TB facility emerged as a major factor in DR-TB treatment initiation and timeliness in our study, similar to other studies in sub-Saharan Africa (SSA).(van de Water et al., 2017, Van Den Handel et al., 2015, Zimri et al., 2012) Patients in some regions were half as likely to be ever initiated on treatment as those in the SW region. Timeliness of treatment did not vary significantly except for two States (Lagos and Osun) where patients were up to 10 times less likely to be treated within 1 month.

Table 10: National and regional characteristics and predictors of early treatment

National and regional characteristics and predictors of treatment within 30 days amongst DR-TB diagnosed patients in 2015										
Individual and Community Level Characteristics	National level					SW Region only				
	Time to Treatment			Predictors		Time to Treatment			Predictors	
	N	<=30 days n(%)	>30 days %	Crude OR (95% CI)	AOR * (95% CI)	N	<=30 days n(%)	>30 days %	Crude OR (95% CI)	AOR* (95% CI)
Sex										
Female	182	92 (50.5)	90 (49.5)	1.0 (reference)	-	73	34 (46.6)	39 (53.4)	1.0 (reference)	-
Male	336	173 (51.5)	163 (48.5)	1.04 (0.73-1.49)	-	121	68 (56.2)	53 (43.8)	1.47 (0.82-2.64)	1.86 (0.93-3.40)
Age Groups										
Age as a continuous variable	46	20 (43.5)	26 (56.5)	0.99 (0.98-1.01)					1.00 (0.98-1.03)	
Children (0-19)	448	235 (52.5)	213 (47.5)	1.0 (reference)	-	19	9 (47.4)	10 (52.6)	1.0 (reference)	
Adults (20-59)	24	10 (41.7)	14 (58.3)	1.43 (0.78-2.64)	-	168	88 (52.4)	80 (47.6)	1.22 (0.47-3.16)	
Seniors (≥60)	46	20 (43.5)	26 (56.5)	0.93 (0.34-2.52)	-	7	5 (71.4)	2 (28.6)	2.78 (0.43-18.04)	
Treatment level										
Community-based	261	112 (42.9)	149 (57.1)	1.0 (reference)	-	83	27 (32.5)	56 (67.5)	1.0 (reference)	-
Facility-based	257	153 (59.5)	104 (40.5)	1.96 (1.38-2.78)	1.77 (1.20-2.61)	111	75 (67.6)	36 (32.4)	4.32 (2.35-7.93)	0.48 (0.14-1.71)
Treatment History										
New	97	58 (59.8)	39 (40.2)	1.0 (reference)	-	18	13 (72.2)	5 (27.8)	1.0 (reference)	-
Retreatment	224	106 (47.3)	118 (52.7)	0.60 (0.37-0.98)	0.59 (0.35-0.99)	104	58 (55.8)	46 (44.2)	0.49 (0.16-1.46)	0.27 (0.07-1.00)
Relapsed	114	65 (57.0)	49 (43.0)	0.89 (0.52-1.55)	0.92 (0.51-1.65)	32	22 (68.8)	10 (31.3)	0.85 (0.24-3.02)	0.60 (0.14-2.56)
Default	57	20 (35.1)	37 (64.9)	0.36	0.47	34	5 (14.7)	29 (85.3)	0.07	0.08

				(0.18-0.72)	(0.23-0.99)				(0.02-0.27)	(0.02-0.41)
Unknown History	26	16 (61.5)	10 (64.9)	1.08 (0.44-2.62)	0.95 (0.37-2.43)	6	4 (66.7)	2 (33.3)	0.77 (0.11-5.61)	0.61 (0.06-6.10)
Type of Resistance										
Mono Resistant	81	38 (46.9)	43 (53.1)	1.0 (reference)	-	21	10 (47.6)	11 (52.4)	1.0 (reference)	
Rif resistant	107	56 (52.3)	51 (47.7)	1.24 (0.70-2.22)		45	22 (48.9)	23 (51.1)	1.05 (0.37-2.97)	
Multidrug resistant	268	140 (52.2)	128 (47.8)	1.24 (0.75-2.04)		100	54 (54.0)	46 (46.0)	1.29 (0.50-3.31)	
Poly resistant	62	31 (50.0)	31 (50.0)	1.13 (0.58-2.19)		28	16 (57.1)	12 (42.9)	1.47 (0.47-4.57)	
Urban/Rural**										
Urban	308	138 (44.8)	170 (55.2)	1.0 (reference)	-					
Semi-Urban	135	88 (65.2)	47 (34.8)	2.31 (1.52-3.51)	2.11 (1.34-3.32)					
Rural	75	39 (52.0)	36 (48.0)	1.34 (0.81-2.21)	1.63 (0.87-3.05)					
Geopolitical zone										
South West	194	102 (52.6)	92 (47.4)	1.0 (reference)	-					
North Central	98	47 (48.0)	51 (52.0)	0.83 (0.51-1.35)	0.72 (0.42-1.23)					
South South	87	42 (48.3)	45 (51.7)	0.84 (0.51-1.40)	0.68 (0.40-1.17)					
North West	70	42 (60.0)	28 (40.0)	1.35 (0.78-2.36)	1.27 (0.70-2.31)					
South East	38	18 (47.4)	20 (52.6)	0.81 (0.41-1.63)	0.73 (0.31-1.70)					
North East	31	14 (45.2)	17 (54.8)	0.74 (0.34-1.59)	0.58 (0.25-1.32)					
States†										
Ogun						53	40 (75.5)	13 (24.5)	1.0 (reference)	-
Lagos						82	23 (28.0)	59 (72.0)	0.13 (0.06-0.28)	0.10 (0.03-0.41)

Osun			10	4 (40.0)	6 (60.0)	0.22 (0.05-0.89)	0.18 (0.03-0.95)
Oyo			49	35 (71.4)	14 (28.6)	0.81 (0.34-1.96)	1.12 (0.44-2.83)

[a] = Continuity Correction and Phi Coefficient
[b] = Pearson Chi-Square and Cramer's V
[c] = Likelihood Ratio and Cramer's V
* Adjusted Odds Ratios (AOR) were obtained by comparing the likelihood of treatment initiation and the time-to-event using the Cox proportional hazard model, adjusted for age, sex, urban/rural or States, or geopolitical zones
**Some correlation was observed between the 'Urb_Rur' and 'States' variables during the test for collinearity, and the Urb_Rur was eliminated in order to build a stronger model
SW=South-West, n=number, OR= Odds Ratio, AOR= Adjusted Odds Ratio, CI=Confidence Interval, Rif=Rifampicin
† *Ekiti and Ondo States had less than 3 patients each and were excluded from the analysis*

These regional differences were likely due to program immaturity and insecurity in some regions compared to others. With the Global Fund (GFATM) supported scale-up of DR-TB services in 2011, the SW saw the first set of reference laboratories, treatment centers with large bed capacities and community treatment enrolment, with patient referrals from other parts of Nigeria. However, another region, the NE, was slow to activate services due to increasing security challenges and frequent insurgent activities between 2013 – 2015, severely hampering healthcare. In the SW, the treatment centre in Lagos State was shut down as a result of the Ebola crisis in 2015 while the treatment centre in Ogun State was not activated until the last quarter of 2015.

Community treatment initiation was rapidly scaled up in the 2nd quarter of 2015 to mitigate challenges patients were facing when admitted to treatment centers away from family for 8 months. Patients had to meet certain criteria such as clinical stability to be eligible for community initiation. The in-patient treatment centers were reserved mostly for children, pregnant women, critically ill patients and those with co-morbidities. This may have contributed to patients in the facility being more likely to initiate timely treatment than those in the community, although community-based management has the potential to reduce treatment delays in similar settings.(Cox et al., 2014)

Since the study period, Nigeria, in collaboration with GFATM and partners, have scaled-up DRTB services to include 29 treatment sites (up from 16 in 2015), 37 GeneXpert sites reference labs (up from 34) and community PMDT in all 37 states (up from 27states in 2015) (Otu, 2013, Gidado et al., 2018). As a result of this, it is likely that average times to treatment initiation are now shorter but new national treatment initiation data have not yet been released. In addition, contextual and multilevel analyses of regional and sub-regional inequalities in access to timely care are needed to inform policy and practice.

The WHO TB Report for 2017 shows that rates of diagnosis and treatment in Nigeria remain low. If the supply end - diagnostic and treatment services - are improving, a corresponding improvement in rates and timeliness of treatment initiation is expected. Where these are not observed, more attention needs to be paid to the demand end- patient sociodemographic characteristics that influence access to care. Further research is needed on the trends in time to treatment in Nigeria, and the patient factors that underlie these.

Study Limitations

Our study had several limitations. Firstly, the excluded 140 patients on treatment could have contributed more to our understanding of timely treatment predictors. Secondly, the two source documents (diagnosis and treatment databases) were not linked with unique patient identifiers and had to be matched manually by other data points. This could have led to some errors in the numbers reported in each category. Finally, due to the retrospective nature of this study, we could not account for the effect of other patient socio-demographic characteristics such as income level, religion and culture, marital status on the risk of being untreated or delayed treatment as this information were not recorded in our source databases.

Preliminary discussions with programme managers, including coauthors of this manuscript, have suggested a range of possible contextual reasons for these state-level differences – including the conversion of the Lagos state DR-TB treatment centre into an Ebola hospital in 2014 - but further research is needed to understand these contextual factors.

Conclusions

Timely access to diagnosis and treatment services are critical to DR-TB patients’ survival and other treatment outcomes. However, within Nigeria, nearly half of diagnosed DR-TB patients are never initiated on treatment, less than a quarter initiate treatment within the recommended 30 days after diagnosis, and regional inequalities in access to DR-TB care are significant. In a context where DR-TB case detection is less than 5% of the estimated burden, these low rates of treatment for cases already detected pose both practical and ethical challenges to DR-TB control. Disparities persist in access to services at patient, facility, and geopolitical levels. Semi-urban and rural residence as well as being initiated in the facility were predictive of earlier treatment initiation, suggestive of complex access challenges. The geographic location of the diagnosing or treatment facility were significantly associated with treatment initiation and timely treatment highlighting significant geopolitical and state differences. The National TB Program needs to strengthen linkages between diagnosis and treatment, as well as provide adequate access and timely treatment initiation for DR-TB patients, especially in the communities, across all geopolitical zones and states.

References

COX, H., HUGHES, J., DANIELS, J., AZEVEDO, V., MCDERMID, C., POOLMAN, M., BOULLE, A., GOEMAERE, E. & VAN CUTSEM, G. 2014. Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *The International Journal of Tuberculosis and Lung Disease,* 18**,** 441-448.

FALZON, D., SCHÜNEMANN, H. J., HARAUSZ, E., GONZÁLEZ-ANGULO, L., LIENHARDT, C., JARAMILLO, E. & WEYER, K. 2017a. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *European Respiratory Journal,* 49.

FALZON, D., SCHÜNEMANN, H. J., HARAUSZ, E., GONZÁLEZ-ANGULO, L., LIENHARDT, C., JARAMILLO, E. & WEYER, K. 2017b. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *European Respiratory Journal,* 49**,** 1602308.

FMOH 2012a. First National TB Prevalence Survey 2012. *Federal Ministry of Health Nigeria*.

FMOH 2012b. First National TB Prevalence Survey Nigeria 2012. *Federal Ministry of Health Nigeria*.

GANDHI, N. R., SHAH, N. S., ANDREWS, J. R., VELLA, V., MOLL, A. P., SCOTT, M., WEISSMAN, D., MARRA, C., LALLOO, U. G. & FRIEDLAND, G. H. 2010. HIV coinfection in multidrug-and extensively drug-resistant tuberculosis results in high early mortality. *American journal of respiratory and critical care medicine,* 181**,** 80-86.

GEHRE, F., OTU, J., KENDALL, L., FORSON, A., KWARA, A., KUDZAWU, S., KEHINDE, A. O., ADEBIYI, O., SALAKO, K. & BALDEH, I. 2016. The emerging threat of pre-extensively drug-resistant tuberculosis in West Africa: preparing for large-scale tuberculosis research and drug resistance surveillance. *BMC medicine,* 14**,** 160.

GIDADO, M., NWOKOYE, N., NWADIKE, P., AJIBOYE, P., ENEOGU, R., USENI, S., ONAZI, J., LAWANSON, A., ELOM, E. & TUBI, A. 2018. Unsuccessful Xpert® MTB/RIF results: the Nigerian experience. *Public health action,* 8**,** 2-6.

GIDADO, M., ONAZI, O., OBASANYA, O., CHUKWUEME, N., ONAZI, M., OMONIYI, A. & ODUSOTE, T. 2014. Assessing the Effectiveness of Xpert MTB/RIF in the Diagnoses of TB Among HIV Smear Negative TB Patients in Nigeria. *Journal of Health Science,* 2**,** 145-51.

MUSTAPHA, G., JUMOKE, O., NWADIKE, P., EMEKA, E., AKANG, G., ENEOGU, R., CHUKWUEME, N., ALIYU, G. & BHATTA, G. 2015. Assessment of Gene-xpert MTB RIF program implementation and the challenges for enhanced tuberculosis diagnosis in Nigeria. *SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS,* 12**,** 1-7.

NBLCP/FMOH 2012. First National TB Prevalence Survey Nigeria. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH 2014. The National Strategic Plan for Tuberculosis Control: Towards Universal Access to Prevention, Diagnosis and Treatment- 2015-2020. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH 2015a. 2015 Annual Report National Tuberculosis and Leprosy Control Programme. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH 2015b. National Tuberculosis, Leprosy and Buruli ulcer Management and control Guidelines. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBS 2016a. DEMOGRAPHIC STATISTICS BULLETIN 2015. . *In:* NATIONAL BUREAU OF STATISTICS NIGERIA, D. D. N. (ed.). Abuja, Nigeria: .

NBS 2016b. National Population Estimates 2006-2016. Abuja, Nigeria: National Bureau of Statistics Nigeria.

ONYEDUM, C. C., ALOBU, I. & UKWAJA, K. N. 2017. Prevalence of drug-resistant tuberculosis in Nigeria: A systematic review and meta-analysis. *PloS one,* 12**,** e0180996.

OTU, A. A. 2013. A review of the national tuberculosis and leprosy control programme (ntblcp) of Nigeria: challenges and prospects. *Annals of Tropical Medicine and Public Health,* 6**,** 491.

PABLOS-MÉNDEZ, A., STERLING, T. R. & FRIEDEN, T. R. 1996. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. *Jama,* 276**,** 1223-1228.

TOPE, A. T., THOMAS BENJAMIN, T., AGU GEORGIA, C. & ABIODUN ABIGAIL, T. 2014. Can Nigeria sustain the fight against drug resistant mycobacterium tuberculosis. *Journal of Microbiology Research,* 4**,** 72-7.

TURETT, G. S., TELZAK, E. E., TORIAN, L. V., BLUM, S., ALLAND, D., WEISFUSE, I. & FAZAL, B. A. 1995. Improved outcomes for patients with multidrug-resistant tuberculosis. *Clinical Infectious Diseases,* 21**,** 1238-1244.

VAN DE WATER, B. J., PRVU BETTGER, J., SILVA, S., HUMPHREYS, J., CUNNINGHAM, C. K. & FARLEY, J. E. 2017. Time to drug-resistant Tuberculosis treatment in a prospective South African Cohort. *Global pediatric health,* 4**,** 2333794X17744140.

VAN DEN HANDEL, T., HAMPTON, K., SANNE, I., STEVENS, W., CROUS, R. & VAN RIE, A. 2015. The impact of Xpert® MTB/RIF in sparsely populated rural settings. *The International Journal of Tuberculosis and Lung Disease,* 19**,** 392-398.

WHO 2006. WORLD HEALTH STATISTICS 2006,.

WHO 2013. Definitions and reporting framework for tuberculosis–2013 revision.

WHO 2016. Global tuberculosis report 2016.

WHO 2018. *Global tuberculosis report 2018*, World Health Organization.

ZIMRI, K., HESSELING, A. C., GODFREY-FAUSSETT, P., SCHAAF, H. S. & SEDDON, J. A. 2012. Why do child contacts of multidrug-resistant tuberculosis not come to the assessment clinic? *Public Health Action,* 2**,** 71-75.

Supplementary Files- Article 3

3A: Variables in the Diagnosis Database (GX Alert)

3B: Variables in the Treatment Database (E-TB Manager)

3C: Estimated TB/DR-TB Case Notification Rates- National and Regional

3A: Variables in the Diagnosis Database (GX Alert)

Patient ID	Test Notes		** Age groups	Test Facility	**Type of Diagnosis Facility	Test State	**Geopolitical zone	**Urban/Rural	Test Date	**Test Quarter	***Treatment initiated
	*Age	*Sex									

* The variables – age and sex- were created from the information recorded in the test notes

** Recoded variables

*** Derived after data linkage to treatment database

For additional information about this database, go to www.ntblcp.org.ng/

3B: Variables in the Treatment Database (E-TB Manager)

Patient ID	Sex	Age	* Age groups	Registration unit	*Treatment level	Geopolitical zone	Registration State	Urban/ Rural	Date of registration	Diagnosis date	Treatment Start date	Type of resistance	Treatment history

* Recoded variables

** After data linkage with the diagnosis database

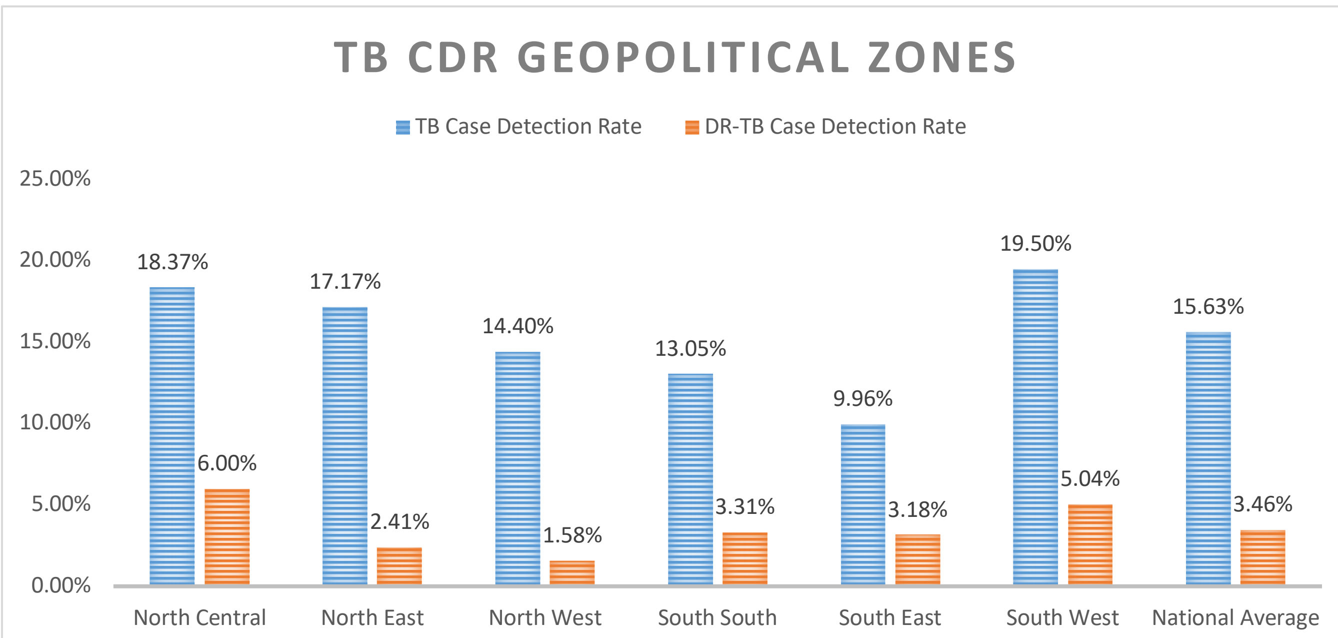
Excluded variables- Patient name, patient address, First medical examination date, Treatment end date, initial weight, case definition, type of disease, number of previous TB treatment, site of disease, registration local government (LGA)

For additional information about this database, go to www.ntblcp.org.ng/

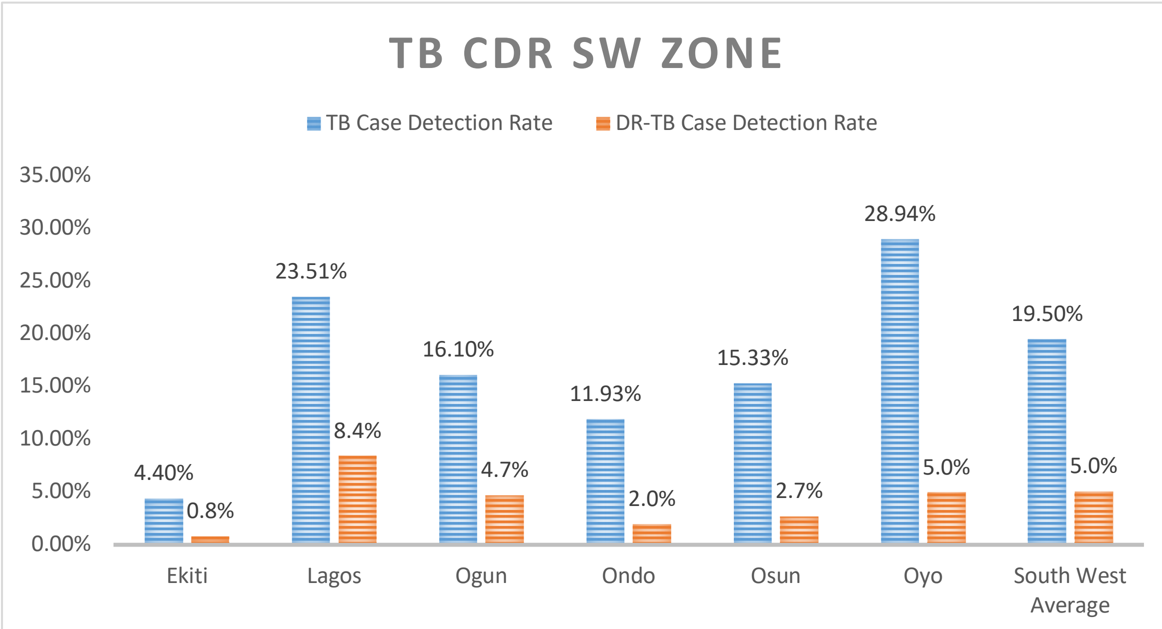
3C: Estimated TB/DR-TB Case Notification Rates- National and Regional

Using study DR-TB data on number of diagnosed patients per state were used to calculate DR-TB case notification rates based on 2015 estimates; These were compared with the National TB case notification rates for the same year and it showed significant regional differences below.

National Level: All TB and DR-TB CDR by Geopolitical Zones in Nigeria



State level in South-West Zone- All TB and DR-TB CDR by South-Western States of Nigeria


TB CDR SW ZONE
TB Case Detection Rate
DR-TB Case Detection Rate
35.00%
30.00%
25.00%
20.00%
15.00%
10.00%
5.00%
0.00%
4.40%
0.8%
23.51%
8.4%
16.10%
4.7%
11.93%
2.0%
15.33%
2.7%
28.94%
5.0%
19.50%
5.0%
Ekiti
Lagos
Ogun
Ondo
Osun
Oyo
South West Average

Article 4: DR-TB Care Cascade

Title Page

Title: Understanding the Gaps in DR-TB Care Cascade in Nigeria: a sequential mixed-method study

Corresponding author: Charity Omenka

Charity Oga-Omenka[1,2,3], Jody Boffa[4,5], Joseph Kuye[6], Patrick Dakum[7,8], Dick Menzies[3,9], Christina Zarowsky[1,2,10]

1. The School of Public Health of the University of Montreal (ÉSPUM), Montreal, Quebec, Canada
2. Centre de recherche en santé publique, Université de Montréal (CReSP), Canada
3. McGill University International TB Centre, Montreal, Quebec
4. Dahdaleh Institute for Global Health, York University, Toronto, Canada
5. Centre for Rural Health, School of Nursing and Public Health, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
6. National Tuberculosis and Leprosy Control Program, Abuja, Nigeria
7. Institute of Human Virology, Nigeria
8. University of Maryland School of Medicine, Baltimore, MD, USA.
9. Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada
10. School of Public Health, University of the Western Cape, South Africa

Keywords:

TB Care Cascade, Nigeria, Access to healthcare, drug-resistant tuberculosis, mixed-methods, diagnosis and treatment.

Funding:

COO received funding for field work through the Global Fund New Funding Model MDRTB Grant (Global Fund to Fight AIDS, Tuberculosis and Malaria: NFM MDRTB Grant), with funds provided through IHVN as the Principal Recipient. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Status: This article has been published in the Journal of Clinical Tuberculosis and Other Mycobacterial Diseases in October 2020.

DOI: https://doi.org/10.1016/j.jctube.2020.100193

ABSTRACT

Background

Despite the availability of free drug-resistant tuberculosis (DR-TB) care in Nigeria since 2011, the country continues to tackle low case notification and treatment rates. In 2018, 11% of an estimated 21,000 cases were diagnosed and 9% placed on treatment. These low rates are nevertheless a marked improvement from 2015 when only 3.4% were diagnosed and 2.3% placed on treatment of an estimated 29,000 cases. This study describes the Nigerian DR-TB care cascade from 2013-2017 and considers factors influencing gaps in care.

Methods

Our study utilized a mixed-method design. For the quantitative component, we utilized the national diagnosis and treatment databases, as well as the World Health Organization's estimates for prevalence to construct a 5-year care cascade: numbers of patients at each level of DR-TB care, including incident cases, individuals who accessed testing, were diagnosed, initiated treated and completed treatment in Nigeria between 2013 and 2017. Using retrospective data for patients diagnosed in 2015, we performed the Fisher's exact test to determine the association between patient (age and gender) and provider/patient (region-north or south) variables, permitting a closer look at the gaps in care revealed across the 5 years. Barriers to care were explored using framework thematic analysis of 57 qualitative interviews and focus group discussions with patients, including 5 cases not initiated on treatment from the 2015 cohort, treatment supporters, community members, healthcare workers and program managers in 2017.

Results

A 5-year analysis of cascade of care data shows significant, but inadequate, increases in overall numbers of cases accessing care. On average, between 2013-2017, 80% of estimated cases did not access testing; 75% of those who tested were not diagnosed; 36% of those diagnosed were not initiated on treatment and 23% of these did not finish treatment. In 2015, children and patients in Northern Nigeria had odds of 0.3 [95% CI 0.1-0.7] and 0.4 [0.3-0.5] of completing treatment once diagnosed; while males were shown to have a 1.34 [95% CI 1.0-1.7] times greater chance of completing treatment after diagnosis. The main themes from qualitative data identified barriers to care along the care cascade at individual, family and

community, as well as health systems levels. At the individual level, a lack of awareness of the true cause of disease and the availability of 'free' care was a recurring theme. Family interference was found to be a particular challenge for children and women. At the health system level, low index of suspicion, lack of rapid diagnostic tools and human resource shortages appeared to limit patients' access.

Conclusions

Any gains in diagnostic technology and shorter regimens are lost with inadequate access to DR-TB services. The biggest losses in the Nigerian cascade happen before treatment initiation. There is a need for urgent action on identified gaps in the DR-TB cascade in order to improve care continuity at multiple stages, improve health service delivery and facilitate TB control in Nigeria.

Introduction

Rifampicin- or multidrug-resistant tuberculosis (DR-TB) actively infected an estimated 484,000 people and took 214,000 lives in 2018, threatening to reverse years of advances in global TB prevention and control (WHO, 2019b, Pai, 2019, World Health Organization, 2019). Drug resistance is an ongoing challenge, especially in settings where healthcare systems are fragmented, suggesting gaps in the care cascade (Gupta-Wright et al., 2018, World Health Organization, 2019).

Nigeria accounts for 4% of the global DR-TB burden and 27% of the incidence in Africa (World Health Organization, 2019). While the World Health Organization (WHO) estimates that 4.3% of new and 15% of previously-treated people with TB in Nigeria have drug-resistant TB (World Health Organization, 2019), others have suggested that the incident rate of DR-TB is much higher (Onyedum et al., 2017, Gehre et al., 2016). In a meta-analysis of 8,002 adult TB patients from across the country, Onyedum et al found 32% of new (734/2,892) and 53% of previously treated people (1,467/5,020) had DR-TB (Onyedum et al., 2017). Gehre et al found 32% (9/28) and 66% (58/88) respectively in Lagos state (Gehre et al., 2016).

Furthermore, Nigeria has particularly low notification and treatment rates of DR-TB. WHO estimates that only 11% of people with DR-TB were diagnosed and 9% placed on treatment in 2018, compared to the 39% diagnosis and 32% treatment rates globally (WHO, 2019a). The 2012 Nigerian National Survey found 75% of smear-positive cases presented with TB symptoms meeting the National criteria for screening (cough for two weeks or more) who had not been previously diagnosed, reflecting some missed opportunities for TB diagnosis (WHO, 2019a, NTBLCP, 2012). According to the WHO, Nigeria contributes 12% of the global DR-TB diagnosis gap, defined as the gap between the number of new cases reported and the estimated incident cases (WHO, 2019a).

In order to meet the End TB targets, Nigeria's diagnosis rates and treatment coverage need to be 90% or more with a drug susceptibility testing (DST) coverage of 100% (World Health Organization, 2019). The TB care cascade outlines a series of necessary steps and services each patient must go through to achieve a positive health outcome. This includes accessing testing, receiving a diagnosis, initiating treatment, completing treatment and surviving at one year of follow-up (Subbaraman et al., 2019b).

Identifying gaps in the DR-TB care cascade in a given setting enables targeted interventions at the stages of the care cascade where losses and drop-outs occur most frequently. Currently, information on factors contributing to gaps in DR-TB care in Nigeria is limited. Our study aimed to estimate the gaps along the DR-TB care cascade and to identify barriers to care from the perspectives of patients, their relatives and DR-TB care providers in Nigeria.

Methodology

Study Setting

National and TB program context

Nigeria, with an estimated 193 million people in 2016 (NBS, 2017), has 36 States and one Federal Capital Territory, across 6 geopolitical zones: North-Central, North-East, North-West, South-East, South-South and South-West (National Bureau of Statistics, 2016). In 2016, there were an estimated 34,140 health facilities in Nigeria- with 88% of them primary, 11% secondary and 0.13% tertiary (Makinde et al., 2018, PharmAccess, 2016). Of these, 67% were public-funded and 33% private sector health facilities, excluding patent medicine vendors (PMVs) and private pharmacies (Makinde et al., 2018). In terms of geopolitical distribution of health facilities, the North-East had 18.6, North-West 14.4, North-Central had 25.8, South-West 20.4, South-East 23.4 and South-South 14.0 health facilities/100,000 population (Makinde et al., 2018).

Although only 33% of treatment facilities were privately owned, studies found that 66-92% of the time, new TB patients visited private providers as their first point of initial care-seeking for respiratory conditions and fever (Organization, 2018, Ukwaja et al., 2013d). Patients, after onset of symptoms, visited PMVs (79%), traditional healers (10%), and private hospitals (10%) (Ukwaja et al., 2013d). Despite this, only 11% of total TB notifications come from the private sector, or less than 3% of estimated incidence (Organization, 2018).

Nigeria adopted the use of GeneXpert MTB/RIF (Xpert) technology in 2011 in several national reference laboratories, increasing access to DR-TB diagnosis (Gidado et al., 2014, Tope et al., 2014). Prior to this, diagnosis for TB relied mostly on smear microscopy, culture, molecular line probe assay and drug susceptibility testing (NTBLCP, 2014, NTBLCP, 2012). Initially, GeneXpert use was reserved for testing HIV patients, presumed DR-TB cases, children, and extra pulmonary TB cases (NTBLCP, 2015a, Cazabon et al., 2017b). Treatment for DR-TB patients began with a hospital-based model in 2010 and evolved to include community-based DR-TB treatment initiation in 2013 (Gidado et al., 2014, NTBLCP, 2014). By the end of 2015, the country had scaled GeneXpert testing to 201 sites, from 7 sites in 2011, expanded testing algorithms to include all presumed TB cases, implemented DR-TB treatment in facilities within 16 States and community DR-TB initiation in 27 States, with support from the Global Fund and other partners (NTBLCP, 2015a, NTBLCP, 2014). At the end of 2015, 12% of Gene Xpert sites and 16% of DR-TB hospital bedspaces were in 3 privately owned facilities (NTBLCP, 2015a).

Study data sources and contexts

Secondary quantitative data were derived from national databases for diagnosis and treatment collected by the National TB and Leprosy Control Program.

The qualitative interviews were conducted in the South-West and North-Central geopolitical zones. Patient and provider interviews were conducted in 2017 from two of the largest DR-TB treatment centers in Nigeria, with 48 and 34 beds, respectively: Sacred Heart Hospital in Ogun State and the Jos University Teaching Hospital in Plateau State.

Study Design and Methods

Our sequential mixed-methods study *(figure 14)* utilised the following methods: a review of Nigeria's DR-TB cascade over 2013-2017 using data from WHO Global TB Reports (WHO, 2014b, WHO, 2015d, WHO, 2016a, WHO, 2017b, WHO, 2018b), a cohort analysis of patients diagnosed in 2015, and a qualitative study based on semi-structured individual interviews with a purposive sample of respondents. We used the Mixed Methods Appraisal Tool (MMAT) [43] to conceptualize, develop and interpret findings from this study (Hong et al., 2018).

The purpose of this sequential transformative mixed methods study (Creswell et al., 2003) was to understand the health system and patient barriers and facilitators to the DR-TB care cascade. The quantitative phase explored health system and patient factors associated with gaps in the DR-TB care continuum. The qualitative phase enhanced the understanding of the health system and patient-related factors for these gaps.

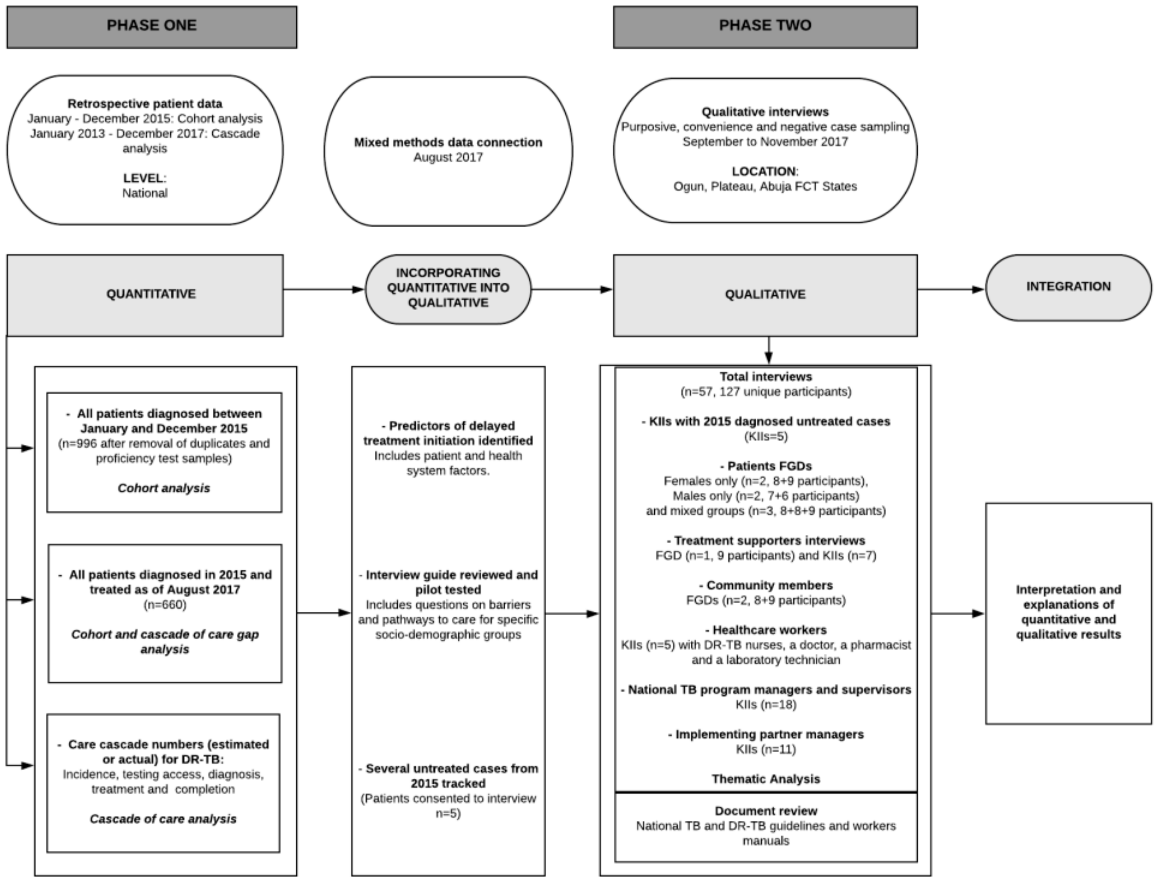


Figure 14. – Mixed-methods sampling strategy

Quantitative data collection and analysis

The WHO TB Nigeria estimates used national TB prevalence (2012) and DR-TB (2010) surveys, Standard and Benchmark Assessment (2013, 2017), and TB notifications (2000-2018) (Glaziou et al., 2016). We elected to analyse the 2015 cohort of diagnosed patients because this was the most recent year with available, complete, cleaned and deduplicated treatment outcome data from DR-TB in the national treatment register, allowing for further insights on gaps in care revealed across the 5 years. The primary results of this analysis have been published elsewhere (Oga-Omenka et al., 2019).

We used two approaches to describe the DR-TB care cascade according to categories outlined by Subbaraman (Subbaraman et al., 2019b). As a first step, we extracted the following data for Nigeria from annual WHO TB reports from 2013-2017 (WHO, 2014b, WHO, 2015d, WHO, 2016a, WHO, 2017b, WHO, 2018b) utilising a denominator-numerator unlinked methodology

(Subbaraman et al., 2019b, Haber et al., 2016): 1) Estimated DR-TB incident cases (defined by the WHO as the TB cases arising in a given time period, usually one year), 2) Number of individuals with DR-TB who accessed TB tests, 3) Number of individuals with DR-TB who were successfully diagnosed as having drug-resistant TB, 4) Number of individuals registered on DR-TB treatment and 5) Number of patients who completed TB treatment. Recurrence-free survival, the final step of the TB care cascade, was not included as there was insufficient data to measure this. Unlike other years, DR-TB incident cases for Nigeria were not explicitly stated in the WHO annual reports for 2013 and 2014 (WHO, 2014b, WHO, 2015d). Rather, we calculated DR-TB incidence based on the 2.9% of new TB events estimated by the WHO for these years. National program data is disaggregated for age, sex and geopolitical zone. We used notification data to describe the same for incidence and testing access (NTBLCP, 2015a). The outcome indicators, including sources of data are described in the *Supplementary file.*

Our second approach is cohort-based, and is a denominator-denominator linked method (Subbaraman et al., 2019b, Haber et al., 2016). Recurrence-free survival was also not included because of a lack of data. The additional retrospective data was collected from 2 different web-based databases for all patients diagnosed with DR-TB in 2015. The diagnosis (GxAlert) receives results from Xpert machines on diagnosed patients. The e-TB Manager database has records for all patients placed on TB treatment. Treatment initiation records were tracked from January 2015 to August 2017 (20-32 months after diagnosis). Preparatory processes, including the handling of missing data, have been discussed in a prior publication (Oga-Omenka et al., 2019).

We utilised VassarStats, a computational statistics website, (www.vassarstats.net) to perform descriptive statistics and tests for association. We used Pearson's chi-squared test to determine associations and Fisher's exact test to compare differences between categorical variables.

Qualitative data collection and analysis

Our qualitative study involved interviews of patients, relatives, and providers in Ogun and Plateau states, as well as program managers in Benue and Abuja, the Federal Capital Territory (FCT). A total of 57 interviews were conducted in these States, including 10 focus group discussions (FGDs), 12 key informant interviews (KIIs) - including 5 phone interviews - and 35 in-depth interviews (IDIs). The five (5) phone interviews were conducted using contact information for patients who were diagnosed but whose treatment start dates were not found in the treatment register to contrast with patients who were already on treatment. There were a total of 127 unique interviewees (*figure 14*).

We asked providers to describe the program structure, challenges and strengths, as well as their perception of access barriers and facilitators. Patients and their treatment supporters were asked to describe barriers and facilitators to accessing DR-TB care that they, their relative or someone they knew had experienced. Community interviews explored common beliefs and practices around TB among the general population. We grouped themes into the different stages of DR-TB care based on participants description of barriers and facilitators they faced as they navigated the care process, although they were not specifically asked to match these factors to all the stages.

Government and program managers at the central level were asked about national policies and resources available for DR-TB control and how these resources were distributed nationally and within each State. They were also asked about the strengths and challenges within the program and how these might have affected different groups of patients.

All interviews were conducted between September and November 2017 by CO, using interview guides developed by the research team and piloted at the beginning of the data collection. Initial entry meetings were held with national and state coordinators, as well as clinic managers at both treatment meetings to discuss overall objectives of the research and sampling strategies. Participants were selected based on their role in the DR-TB program and availability during the interview timeframe. Informed consents were written or verbally acknowledged before each interview. All interviews with patients were conducted outdoors in the treatment centers with patients who had been on treatment for more than two weeks. Interviews were conducted in English and respondents were encouraged to respond in or ask for translation into Nigerian pidgin, Yoruba or Hausa as needed. Interviews were audio-recorded and transcribed. There were instances of responses translated from the Yoruba language, the predominant language in the South West of Nigeria and pidgin English by translators fluent in those languages. Transcripts were sent back to 17 participants who had earlier agreed to be contacted for accuracy checking. Six participants responded, with 2 requesting minor revisions, and transcripts were revised accordingly prior to analysis.

We used a framework approach involving both inductive and deductive thematic analysis (Gale et al., 2013). Codes were inductively derived and assigned to new themes or deductively derived from themes identified from an initial systematic review of barriers and facilitators to DR-TB care (Oga-Omenka et al., 2020c). Interviews were coded by the first author (CO) with the help of 2 assistants. All themes and codes were double-checked by CO. Other members of the research team checked the thematic analysis for overall alignment with study objectives. Transcripts were coded with aid of Quirkos software, version 1.6.1.

The research team comprised two senior scientists (CZ and DM) with extensive experience in social, implementation science and TB research; a PhD researcher (CO) and post-doctoral fellow (JB) with over 15 years of combined implementation and mixed-methods research experience in HIV/AIDS and TB in sub-Saharan Africa; a DR-TB National program manager (JK), implementing partner and seasoned researcher in Nigeria (PD); and a research assistant who was a recent science graduate fluent in Yoruba and the pidgin English widely spoken in Nigeria. The research assistant was trained for 2 weeks on qualitative interview skills before fieldwork. None of the researchers were directly involved in patient management for DR-TB.

Ethics

The National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007) and the Research Ethics Committee (CER) of the University of Montreal Hospital (17.060) granted ethical approval for this study. An additional ethical approval was obtained from the Research Ethics Committee (CER) of sciences and health of the University of Montreal (CERSES-19-098-D). All interview participants gave written or verbal informed consent.

Results

Quantitative results

Changes in DR-TB Care Cascade in Nigeria, 2013-2017

Our data show a gradual increase in numbers retained across all stages of the cascade between 2013 and 2017. Graphs showing each stage of the DR-TB care cascade from 2013-2017 are described in more detail below.

Estimated incidence varied between 2013-2017 due to differences in measurements (*Supplementary file*). According to the WHO, Nigeria DR-TB incidence estimates fell from 29,000 in 2015 to 20,000 in 2016 (a reduction of 32%) when data on the prevalence of HIV among prevalent TB cases derived from the 2012 national prevalence surveys from Nigeria was used to re-estimate TB incidence ((WHO, 2017b), p.24). We have elected to use a 5-year average of estimated incidence (*figure 15*).

The increases in cases diagnosed and treated over the 5 years was statistically significant ($p<0.0001$). In step 5, treatment success rate stayed relatively the same from 76.9% in 2013 to 76.7% in 2016. Data were unavailable on the number of patients diagnosed in 2017 who completed treatment.

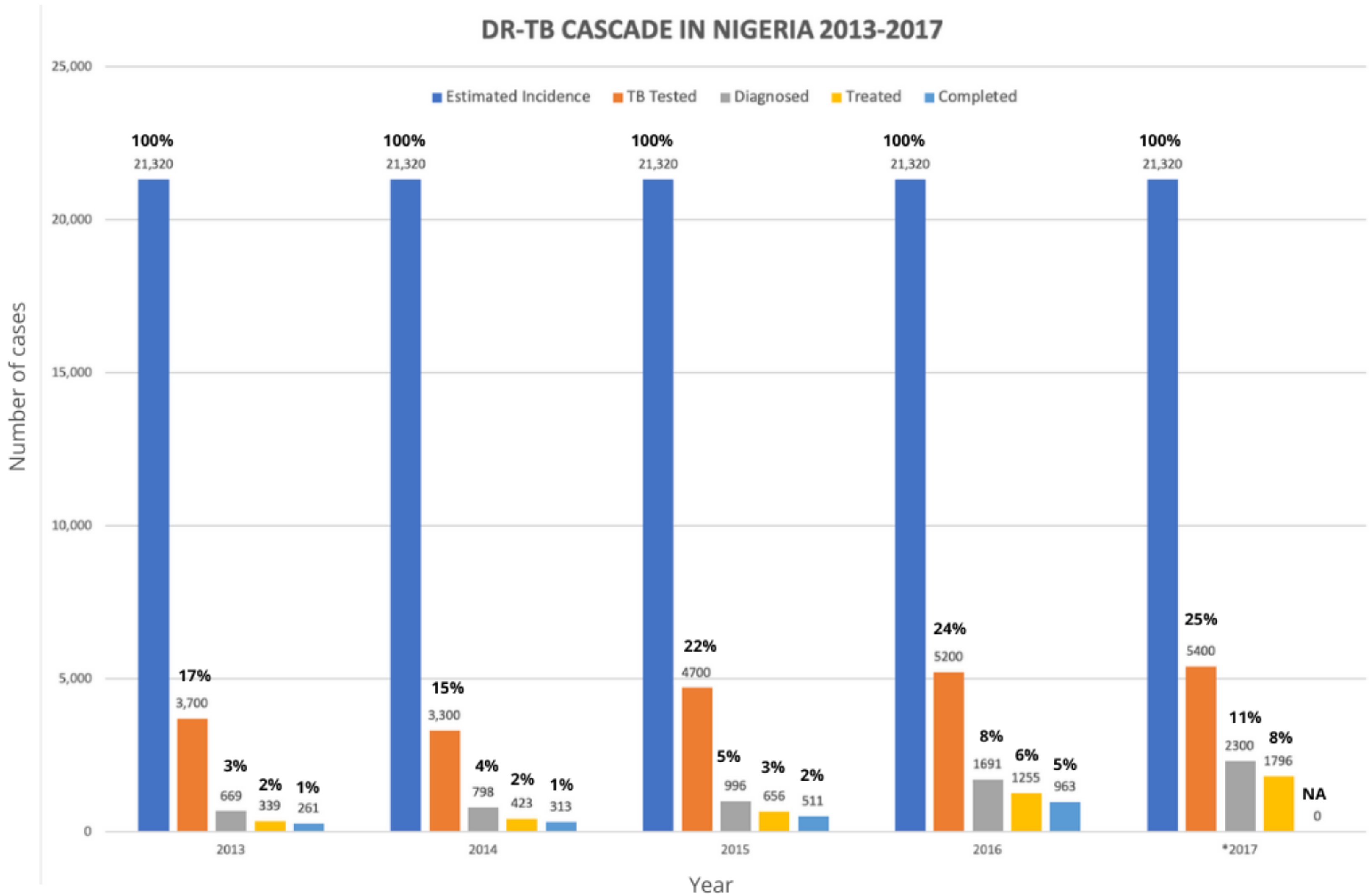


Figure 15. – Trends in DR-TB Care Cascade in Nigeria 2013-2017

Percentage retained, which is the ratio between patients who completed treatment and the estimated incidence for the year, increased from 1.5% to 4.8% between 2013 and 2016, representing a 3-fold increase.

The percentage losses between each stage of care are shown in *Figure 16*. On average, between 2013 and 2016, 80% of estimated DR-TB patients did not gain access to testing for TB or drug susceptibility. Three-quarters of those who were tested were never diagnosed. Of those diagnosed, 35% were not initiated on treatment, and 23% of those treated did not complete treatment. The biggest losses over these years were in testing and diagnosis access, as more than 60% of those diagnosed were treated, and went on to complete their treatment.

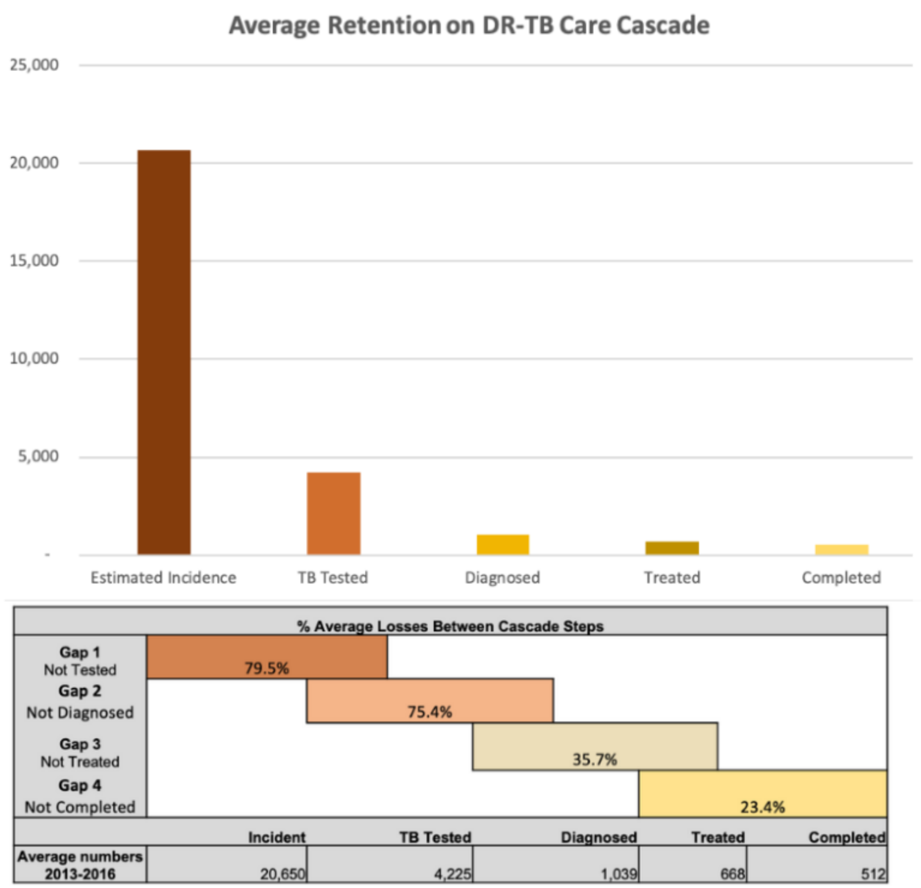


Figure 16. – Average Retention and Losses in DR-TB Care Cascade in Nigeria

Characteristics of patients within the DR-TB Care Cascade in 2015

Data sources for the cascade steps and gaps for patients diagnosed in 2015 are shown in *Table 11.*

Table 11 Data sources for the cascade steps and gaps for patients diagnosed in 2015

Cascade step	Estimation/data source (reference)	DR-TB n (95% CI)	Gap	Interview data source
1. Estimated Incidence	• WHO estimation based on country prevalence surveys (WHO, 2016a) • National drug resistance survey (2010) • National TB prevalence survey (2012) (NTBLCP, 2012) • NTP program data (2015)(NTBLCP, 2015b, NTBLCP, 2015a)	29,000 [15,000-43,000]	1: Number of individuals with TB who did not reach health facilities and access a TB diagnostic test	• Community members and families of individuals who died of probable DR-TB • Pathways of individuals on DR-TB treatment • Providers of DR-TB care at the health center and community levels
2. Accessed testing for any TB (reached TB centre)	• Percentage notified for any TB who were tested for rifampicin resistance (WHO, 2016a) • National reference laboratory data • NTP case notification data (NTBLCP, 2015a)	50,274 [-]	2: Number of individuals with TB who accessed a TB diagnostic test but did not get successfully diagnosed	• Community members and families of individuals who died of probable DR-TB • Pathways of individuals on DR-TB treatment • Providers of DR-TB care at the health center and community levels
	• WHO TB estimate of DR-TB among notified pulmonary TB cases (WHO, 2016a) • NTP case notification data (NTBLCP, 2015a)	4700 [3700-5700]		

3. Diagnosed	• National Gene Xpert database (NBLCP/FMOH, 2015b) • NTP case notification data 18)	996 [-]	3: Number of individuals diagnosed with TB who did not get initiated in treatment	• Gene Xpert (diagnosis) database • Individuals on DR-TB treatment • Community members • Providers of DR-TB care at the health center and community levels
4. Initiated on treatment	• National e-TB (treatment) database (NBLCP/FMOH, 2015a) • WHO (WHO, 2016a)	660 [-]	4: Number of individuals who did not complete TB treatment (due to treatment failure, loss to follow-up, or death)	• Community members of individuals who did not complete DR-TB treatment • Providers of DR-TB care at the health center and community levels
5. Treatment completed	• National e-TB (treatment) database (NBLCP/FMOH, 2015a) • WHO (WHO, 2016a)	511 [-]	5: 5: Number of individuals who experienced post-treatment TB recurrence or death	No data

The DR-TB diagnosis and treatment data for 2015, disaggregated by age, sex and geopolitical location, gives a closer look into the gaps in care (Table 12). Among the 29,000 people estimated to have to TB of any form in 2015, 4700 were estimated as DR-TB cases among notified pulmonary TB cases. The WHO estimates these as the DR-TB patients expected to be found among all notified pulmonary TB patients for a given year, if all notified pulmonary TB patients were tested for RIF-resistance using WHO-recommended diagnostic tests (Organization, 2020). This is different from the absolute number of patients tested for DR-TB (with or without a positive result) in the year. Subbaraman et al, 2019 (Subbaraman et al., 2019b) (*Table1*) recommends using this estimate of DR-TB among notified pulmonary TB cases as a proxy for the total number of DR-TB patients who likely accessed testing during the same period. Of these, 996 were diagnosed with DR-TB, 660 were treated and 511 completed treatment.

Table 12: Characteristics of patients within each stage of the care cascade in 2015

Characteristic		**Estimated Incidence*	**Estimated Tested*	*Diagnosed*	*Treated*	*Completed*	*Pearson X^2 p-value*	*Diagnosed Vs Completed Fisher's exact test*
TOTAL		n (%)	n (%)	n (%)	n (%)	n (%)		OR [95% CI]
		29,000	4,700	*996*	*660*	511		
Age	*Children (0-14)*	*3,316 (11.4)*	*248 (5.3%)*	*26 (2.6)*	*8 (1.2)*	*8 (1.4)*	0.0685	0.2989 [0.1287-0.6941]
	Adults (>14)	25,686 (88.6)	*4,453 (94.7)*	*970 (97.4)*	*652 (98.8)*	*580 (98.6)*		
Sex	Male	17,568 (60.6)	2,882 (61.3)	647 (65.0)	444 (67.3)	398 (67.7)	0.4527	1.338 [1.028-1.741]
	Female	11,432 (39.4)	1,819 (38.7)	349 (35.0)	216 (32.7)	190 (32.3)		
Geopolitical region	North	50,225	2,606	460	239	206	0.0004	0.4032 [0.3118-0.5215]
	South	40,359	2,094	536	366	358		

* Not included in the Pearson X2 test of association or the Fisher's exact test as these numbers are estimates

The association between age, sex and geopolitical zone and progression through the cascade of care was shown to be statistically significant. Using the Fisher's exact probability test, children had lower odds than adults (0.3, 95% CI 0.1-0.7), males had 1.34 (95% CI 1.0-1.7) greater odds than females, and patients in the north had lower odds than those in the south (0.4, 95% CI 0.3-0.5) to move from diagnosis to treatment completion. A further analysis of this cohort are presented in a previous publication (Oga-Omenka et al., 2019).

Qualitative results

Factors influencing gaps in care

Our qualitative analysis focused on the first four cascade of care steps – testing access, diagnosis, treatment initiation and completion. From the perspective of patients and treatment supporters, several factors influenced access to care at each stage of the cascade. The interviews with providers were mostly in agreement with the factors identified by patients and their relatives.

Our results presented below and in *Figure 17*, group themes influencing each stage of the care cascade into individual/patient factors, interpersonal influences operating at the family or community level, and finally at the health system level. We present several examples, especially for testing and diagnostic gaps, which were identified as the major barriers in the quantitative results.

Summary factors influencing DR-TB care cascade

	INDIVIDUAL FACTORS	INTERPERSONAL INFLUENCES	HEALTH SYSTEM FACTORS
STEP 1: TESTING	• Awareness of available services • Symptom minimization • Use of traditional medicine • Self-medication • Poverty • Geographic location	• Recommendation from a trusted person • Stigma and discrimination • Patients and relatives as community advocates • Hard-to-reach communities	• Low index of suspicion • Costs of pre-diagnosis work-up • Lengthy care procedures • Clinical misdiagnosis • Lost time to wrong treatments • Lack of resistance testing in the private sector • Stigma and discrimination
STEP 2: DIAGNOSIS	• Cost of transportation • Impatience with testing delays • Persistence and agency • Fear of a positive diagnosis	• Community misconceptions about disease and healthcare	• Provider knowledge • Sputum transportation • Laboratory procedures • Clinic procedures • Stigma and discrimination
STEP 3: TREATMENT	• Denial • Fear of medication side effects • Desire for quicker resolution • Concern for family • Fear of losing livelihood • Lost to follow-up and death	• Family support • Treatment supporter • Disclosure • Cultural beliefs	• Patient financial support • Lengthy pre-treatment procedure • Coverage of treatment facilities
STEP 4: COMPLETION	• Medication side effects • Hopelessness and depression • Fear of losing livelihood • Lost to follow-up	• Family support • Treatment supporter	• Medication side effects • Treatment duration • Patient tracking
CROSS-CUTTING	• Missed appointments • Attribution of symptoms to other causes • Preference for traditional or faith-based care • Misconceptions of healthcare • Death	• Husband's permission • Parental authority • Religious leader influence • Work and family commitments	• Coverage and level of service • Patient counseling • Inadequate health worker numbers, skills, attitude and motivation • Health information- poor linkage and referral, data errors • Stockouts of health products • Inadequate health worker resources and support

Figure 17. – Summary factors influencing DR-TB care cascade

Gap 1: Accessing to TB diagnostics

Many respondents described individual delays in accessing testing. Predominantly, this related to a number of uncertainties about TB and to symptom minimization, being unaware of available care and the use of alternative care as a first option. For example, one FGD participant indicated:

"For me, when I started coughing, I was thinking that maybe it's [a] normal cough, two and three days, you use [cough syrup] and it will go…".

Others were unclear about where to get tested:

"…this TB is killing people a lot. For many people that I know, realising later that it was this sickness that killed [them], and they did not know of this centre or to go to another centre" (Patients FGD).

For many, initial care seeking involved alternatives to the public sector. For example, many patients or their loved ones described first seeking care through “prayer houses,” traditional healers, or through the private sector:

“[When this illness started], I went to private hospitals, and they did not see anything wrong with me, I went to church and they said it was spiritual attack. Then I went to a [health] centre and they were not straight forward; they did not answer me. I started using different types of herbal mixture for like one month but I had gone round earlier before I got here.” (Patients FGD)

There were also instances of patients resisting further testing. One healthcare worker described patient fears related to long hospital stays if they were found to be positive:

“*We actually want[ed] him to come for [drug resistance] test but some other people [had] …cornered him [to say] by the time you go, they are going to put you in the treatment center and you may not come out till so, so period, so the patient refused [to come back]”*(HCW KII).

When asked what could have helped them or their loved one get earlier access to testing, respondents indicated clearer information about TB and where to access reliable testing services at no cost to patients. One family member described his perspective of care in private hospitals, where he felt his loved one had unnecessarily perished:

‘The problems I have noticed are amongst the private hospitals. They don’t diagnose [when] people have TB. They give wrong medications to people with DR-TB, which worsens their cases. They will be treating malaria, typhoid [fever]… making some mistakes costing people their lives. But, assuming the knowledge of TB is everywhere… it will be easy for [private hospitals] to diagnose and treat it” (Patient relative KII).

All participant groups repeatedly highlighted the need for increased community awareness around TB and availability of free services.

“Before coming here I was not aware … that there is TB care here …[and] that everything is free. I didn’t believe that …my mummy asked if I would come I said no, I was not coming but

[eventually I came and].. [my health] has improved ... The patients coming here are happy … that is why we are suggesting radio advertisement or TV …" (Patient FGD).

"My advice is that there should be awareness through the radio or television that whoever that coughs should visit hospital that it is free because when charges are involved many will run. Many listen to radio in car or homes or television. [Someone can say], my friend you have been coughing for a week and I heard on radio that it is free in the hospital. It will create awareness" (Patient FGD).

Providers also reinforced the need for more awareness, similar to what exists in the HIV program.

"One thing I can say is that, it is just the awareness, for [patients] to know that this TB has to be diagnosed and where to get the treatment... I think that the major thing … that [TB] is existing, and [services] are free. ..." (HCW KII).

"…The awareness is not much, they should …make people aware of TB, like … they did for HIV. …the awareness is not as much as that of HIV. And TB is killing more than HIV" (HCW KII).

Several family and community influences were reported to prevent access to testing. Respondents cited instances in which patients' parents or spouses acted as a barrier to appropriate care, sometimes because of their own beliefs in alternate care, a lack of awareness about the TB symptoms or available services. These are discussed further in cross-cutting themes below.

A number of *health system barriers* were identified including inadequate coverage of services, inadequate human resource, lengthy care procedures, and misdiagnosis due to low index of suspicion in both public and private hospitals. The attitude of public healthcare workers was also a cited as a barrier.

” The first day I went for [a] test. ...they chased me out that I should go and stay by the window…I felt embarrassed ...why should I be disgraced to stay outside ...they ordered me to buy [a] handkerchief to cover my mouth … they chased me away” (Patients FGD).

Gap 2: From testing to diagnosis

Participants mentioned several patient level reasons for difficulty getting diagnosed after testing. A predominant theme was preference for private sector care or long wait times for test results in the public sector, which led to the seeking of alternate care elsewhere. A second important theme was not being able to pay transportation costs to return for appointments.

“I got there for sputum culture, at government hospital they said [for] this [test], you will have to come back for it. They will have to be giving us [a] date to come back for the sputum, they will say come back another day, if you get there again they will say you came late, and this thing is disturbing me up to the extent that I could not walk, people will have to hold me, until they said go somewhere else” (Patients’ FGD).

At the interpersonal level, there were instances of families removing patients from the care cascade to seek alternatives in traditional healing and prayers, or the patients themselves preferring alternative care to the DR-TB care offered publicly. These are discussed in cross-cutting themes below. While these family influences were sometimes negative, there were also responses indicating that parents had to be persistent to get their children diagnosed.

“They did [a] series of tests for her [daughter] and it was saying negative, negative until that thing ate all her lungs and killed her. So, when her [other daughter] started coughing, they were taking her to several hospitals, until they got to general hospital …. [For] months, they asked [the mother] to come back, … she was always going and coming, asking [about] the result [and] they always said nothing. [Much] later, [they] called the mother [with the result]” (Patients FGD).

At the health system level, the predominant themes were prolonged laboratory delays and errors, as well as negative healthcare worker attitudes.

"Sometimes [the problem] is waiting… you brought the sample and … most of time is the DOTS people will not give … accurate … information. They [will] say ...drop your sample in the lab .. and go and … come back tomorrow or come back on Friday, [and] today is [only] Monday…[they will say] come back next week (HCW KII).

"Some [government] hospitals ...were always postponing appointments, treating people like animals...they shout on us not to stand somewhere, touch anything, or ...go out, come back tomorrow, up to the extent that I had given up ... but ... a month after I got the test after disturbing them, but some people do not have the perseverance to do what I did....please help us to explain to [HCWs] to treat [patients] well" (Patients FGD).

Gap 3: From diagnosis to treatment

Barriers to treatment initiation occurred at individual, family and health system levels, many of which were also cross-cutting, such as preference for private sector care. At the individual level, some participants recalled knowing patients who died before they could initiate treatment due to delayed diagnosis. A few instances were cited of patients refusing treatment or giving false addresses because of fear of long treatment duration or belief in alternative care, particularly traditional or spiritual healing.

"Sometimes … there are some people … they [say they] know what their problem is. [They] came to [the hospital but] gave [a] fake address and phone number ... I think this quarter alone … I have lost 3 [patients] like that. The last conversation we had was that they know their problem was [a spiritual attack] from their village and [they] are going to [the church]. … Sometimes [for this] group of people you cannot account for them, because …when you call …the number will not connect" (HCW KII).

There were particular instances of adult females living with their parents, who were prevented from accessing treatment. In one instance, the duration of treatment was a barrier, and the parent thought going to a prayer house would bring faster results. In the other instance, the father believed his daughter was already healed by prayer and not in need of any medication.

Family responsibilities and fear of separation, school and work conflicts were also mentioned as barriers to starting treatment.

At the health system level, limited hospital bed spaces to admit patients in the initial phase of treatment contributed to delays in treatment. HCWs also mentioned staff workload and low motivation, due to unpaid salaries, resulting in slow case management.

"From the provider's side is a lack of motivation. Imagine were you are going to attend to a patient every day for … 20 months, that means you abandon almost all you have to do, for that patient. And in a situation where salaries are not forthcoming and the support from the [funding] partners are [much]. The program pays the DOTS providers [5USD] communication allowance monthly but there is a very good package for the patients [105 USD]. … Most of the providers in the face of no salaries will … envy what the patients are getting... So, from the provider side this is one of the major challenges" (HCW KII).

Gap 4: From treatment initiation to treatment completion

At the individual level, several respondents mentioned that adverse drug reactions were a major issue with adhering to the treatment regimen. These led to some instances of patients losing hope or becoming anxious and refusing further treatment or dying while on treatment.

"[An elderly man], … when he sees the tray for drugs, … he will start vomiting, ha! even when they have not given him, as soon as he sees it, he starts vomiting. … even nurse or doctor, when he sees them he will just start vomiting, and finally he said he wants to go, … if he even sees the color of the doctors or nurses uniform he will be so afraid…he said it is better for him to go [home] and die… maybe he is dead but we don't know. .. they gave him [the] paper to sign out of treatment…and he signed out and left" (Patients FGD).

An initial 8 months hospitalization was the standard practice before 2013 and is still used for certain high-risk patients e.g. pediatric cases and those who are pregnant or have co-morbidities. Transitioning between the initial hospital phase and continuation in outpatient care, was also another point at which patients dropped off treatment, sometimes due to miscommunication or poor understanding of the process.

"...a lack of information caused my stopping the treatment, due to... lapses on their sides... because ... after they discharged me I was [told] to go [to] the community- who are the community I don't know,... [that] is their medical term...[I] am not a medical person. How do I get to know all those things? ...that was how I actually stopped... taking my medication... " (Patients FGD).

Weak linkages and referral systems led to patients dropping off treatment when moving between facility and home. One instance involved a prisoner released from jail who was subsequently lost to follow-up.

Cross-cutting barriers across the care cascade

Several cross-cutting barriers were identified. At the individual level, these included attributing symptoms to other causes, or perceptions about healthcare which led to a preference for alternative care at all levels of the cascade.

The major cross-cutting themes on interpersonal influences were related to the influence of parents, spiritual leaders and to a lesser degree, husbands. Although predominantly negative, these experiences were sometimes positive.

"My pastor, he told me to come to the [treatment center], that this cough I am coughing that he has seen someone that was coughing the same and had been collecting drugs for six month and it stopped, it was my pastor that knew about it and ask me to come." ." (Patients FGD).

"We have had a case of a pastor who refused … a member of his church from taking drugs for DR-TB when the patient actually has DR-TB. He refused vehemently that it was not a disease to be cured like that, that it was a special [problem]. But … eventually [the pastor] himself came down with DR-TB and died" (HCW KII).

Parental influence was a particular problem across the care cascade, affecting even adult patients, especially if they were female. This was often due to the parents own perception of better results with alternative care.

"I had an experience.... a patient ... was ... asked ..to go and do... a [further testing] ....the mother insisted that it is ...a spiritual attack...and all effort to ensure that.. the patient takes treatment, failed" (HCW KII).

In one instance, a phone interview was cut short when the participant, who had not yet initiated treatment, was interrupted by her father, who cut the line after demanding that the interviewer never contact her again. Her brother called the line ten minutes later:

"*The man who spoke with you earlier is [the patient]'s father. God has healed [her], she is totally well now. Her father does not want to hear [from] you or, anyone who talks about DR-TB so, keep off for the sake of peace."* (Relative to patient not initiated on treatment).

Healthcare workers and program managers also mentioned the lack of female autonomy to seek care without their husbands' approval.

"Women… of course, you know some women depend on their husbands… There are [wives] that [can't] go out, even when she is sick… and the husband [might] feel like taking her to the hospital is just … maybe [a] waste [of] time, until the sickness [has made her bedridden]." (HCW KII).

When female patients were asked directly, none of them mentioned that this was a factor. However, one FGDs participant mentioned that her husband's persistence was key to her diagnosis.

At the health system level, predominant themes addressed the attitudes, knowledge and skills of providers, which affected linkage and referral to aappropriate care. This was not always negative, as one participant cited the information given to them by TB officers as responsible for changing community perceptions about TB.

"What we heard about TB before the arrival of [the] TB center is that some wicked people do blow the charm[ed] air ... once it is blown at you, you contract TB but the arrival of TB officer changed our orientation, … that it's not an attack from people but [an] infection" (Community FGD).

Attitudes of healthcare workers, from the perspectives of patients, were predominantly negative before diagnosis.

"When this [illness] started… when I went for [a] test … I was treated anyhow, like sit here, leave here, shouting and I fought them to stop chasing me ... and embarrassing me" (Patients FGD).

Health workers became much more supportive once patients began treatment, and this was the same across interviews from different centers.

"…they are taking [good] care of us. We [get our medications] and collect injections at the right time; if anything happens to us or we feel anything, we go to meet them. They [joke] with us, allowing us to realise that we are still humans, and that there is still hope for us here…" (Patients FGD).

"They attend to us as if we are their [relatives]. There is no stigmatisation… I don't know of other centres but they don't separate themselves [from us here]. If at times we [don't] use our mask, they talk to us …, attend to us. They don't … shout at us [or] make us feel different" (Patients FGD).

The provision of free DR-TB care and patient financial support was mentioned repeatedly by patients and their relatives as the main facilitator to care.

"…when I remember [what I went] through [with] my daughter, how they [referred] us from [one hospital] to [another]. [An] ordinary razor blade, before they will give you … you go and pay in to the [hospital] account … but , I thank God for [the program]. They make me to be the happiest woman on this earth because [to] lose a child of … 15 years [would] not [have been] easy but today they put laughter into my own family… Thank you." (Treatment supporters FGD).

"The day they gave me the result and said it was TB, I was like ah, and I started thinking that where do I want to get money, I told my husband and he was worried. The doctor then said that whatever we are using here will be free of charge…" (Patient FGD).

"I used to hear that they heal people with cough at this place , but I was like, how much will I [pay] there? but when I heard it was free, that was what gave me the opportunity to come here" (Patient FGD).

Program strengths

Overwhelmingly, patients cited the free care and financial support provided by the program as the major facilitators of access, enabling them to focus on getting better, without the added worries of compensating for lost livelihoods due to the effects of the illness itself and workplace stigma. Other strengths of the program were the patient education and counseling sessions.

On the other hand, healthcare workers mentioned teamwork and coordination, pooling of resources from implementing partners, the use of technology e.g. WhatsApp messaging within the team to improve patient tracking and GeneXpert results notifications.

"If there are treatment issues, treatment interruption, so that the community based officers [can intervene] immediately and to also respond. If there are drug reactions you know who to call it could also be the doctor, it could be [someone else]. We already have like a coordinated referral system and also we use the WhatsApp very well where you just throw [in any question] and you can be sure there will be a quick response." (HCW KII)

Discussion

Our mixed methods analysis of the DR-TB care cascade in Nigeria contributes to the understanding of the main factors influencing access and retention in care for DR-TB patients and brings to bear the importance of targeting control efforts at different stages of the care cascade.

Although numbers improved over the period of study, only 2.5% of people with DR-TB successfully navigate the DR-TB care cascade in Nigeria. The vast majority do not even make it to formal providers. Our qualitative data suggests there is a lack of awareness regarding TB in general, and specifically around main symptoms, where and how to access free testing, and that TB is curable with appropriate treatment. However, there was a 3-fold increase in the ratio of patients who completed treatment, and this was likely due to the scale-up of appropriate DR-TB testing (Gene Xpert). This also translating to improved numbers at Steps 3-5 of the care cascade - those who got diagnosed, treated and completed treatment for DR-TB.

Our data sources and design only allow minimal insight into this first step, because cohort and interview data were on patients who were already diagnosed. However, from what participants recalled, accessing testing was difficult mostly because of a lack of awareness. This resulted in seeking private sector care, including with private hospitals, patent medicine stores and traditional healers. Our data suggest that this may relate to how people are treated in the public sector or alternative explanations about what causes the symptoms. However, some patients may be lost to follow-up due to poor linkages between the private and the public sector. Respondents mentioned that knowing someone with knowledge about TB and available services was instrumental in getting them into care, similar to studies from South Africa and India (Naidoo et al., 2015a, Yadav et al., 2015). Interventions to improve program visibility through community awareness, as suggested by the participants, and engaging the private sector, including with spiritual and traditional healers, have been shown to dramatically improve TB case finding (up to 100%) in resource-limited settings like Nigeria (Sharma et al., 2005, Yassin et al., 2013b, Colvin et al., 2014).

Our data suggest an estimated three quarters of DR-TB patients are lost at Gap 2 due to misdiagnosis or inadequate provider index of suspicion, poor provider attitudes, clinic and laboratory challenges and the poor linkages between the private and public sector. Patients also mentioned fear of prolonged treatment. Provider training and supervision contributed to significant increases in case finding in India and Ethiopia (Ambe et al., 2005, Yassin et al., 2013b).

According to the care cascade, the majority of people diagnosed with DR-TB (64%) went on to initiate treatment and 78% of these finished treatments. Gaps 3 and 4, treatment enrolment and completion, were sometimes due to individual beliefs and perceptions about healthcare, and fear of treatment, as well as work and family commitments. This highlights the need to continuously counsel patients, especially on adherence and potential side effects, and to address the opportunity costs of accessing care, as this has been shown to improve retention in care (Law et al., 2019). The financial support given to patients was repeatedly cited as a major facilitator at this stage and needs to be sustained.

Related to treatment completion, patients' mental health and the toll from medication side effects were underscored by several respondents. The toxicities of DR-TB medications and their effects on patients' outcomes is widely documented (Meressa et al., 2015, Deshmukh et al., 2015, Awofeso, 2008). The current revision in WHO guidelines to shorter oral regimens will potentially improve patient adherence to treatment, as side effects reduce (Abidi et al., 2020, WHO, 2019d). Several studies have made a case for psychosocial support for DR-TB patients (Khanal et al., 2017, Kaliakbarova et al., 2013, Thomas et al., 2016).

Although DR-TB incidence was higher in adult males, women and children faced particular challenges in accessing care due to a lack of autonomy and adverse gender norms. Our cross-cutting findings of instances of family members preventing TB care for their family members is not very common in the literature, although some studies have reported marriages ending as a result of a TB diagnosis for the woman (Sharma et al., 2014, Onifade et al., 2010). We found one study in India, where parents prevented their daughter's TB treatment enrolment to avoid stigma and a cancelled marriage (Deshmukh et al., 2015). Other studies from Nigeria have found similar adverse gender roles impeding access to TB care for women (Oshi et al., 2016a, Ibrahim et al., 2014b).

While each level had unique barriers, addressing the cross-cutting barriers could serve as a first step for policy change and targeted interventions. For example, at each level of the cascade, patient beliefs and perceptions about the symptoms and the path to cure determined whether they persisted to treatment completion or not. Patients and providers repeatedly recommended improving community awareness on TB. This would likely have impact across the continuum of care, as evidence from other countries shows (Datiko and Lindtjørn, 2009, Islam et al., 2017). Data management and correctly tracking patients by verifying contact information is another area that could have cross-cutting impact on the cascade of care (Weigel et al., 2011, Stalin et al., 2020).

On the health system level, in addition to improving coverage and access to GeneXpert testing, our findings suggest that training providers to recognize individuals at risk for DR-TB and on stigma and discrimination could play a role in reducing the very large gaps 1 and 2 in the care cascade (Karamagi et al., 2018, Wu et al., 2017). Additionally, healthcare providers felt under-resourced and unsupported to provide adequate care, agreeing with findings in a recent study from India (Thomas et al., 2020).

The significant gaps in accessing testing and diagnostic services noted in our data agrees with findings on DR-TB cascades in India and Madagascar, where Gaps 1 and 2 were reportedly the biggest gaps in DR-TB care (Knoblauch et al., 2020, Subbaraman et al., 2016). These findings are in contrast with the South Africa DR-TB care cascade showing treatment initiation and completion were the biggest challenges (Naidoo et al., 2017).

Our findings suggest TB policy implications. Increasing patient awareness of TB symptoms and available services is an important first step for TB control in Nigeria, since case-finding is reliant on patients recognizing their symptoms and presenting to a public health facility with TB services. This is supported by other studies from Nigeria, calling for improved public communication around TB (Hassan et al., 2017, Jombo and Mbaave, 2018, Babatunde et al., 2015). Mass awareness campaigns have been used successfully in South Africa and other settings to create awareness, reduce stigma, and improve case finding(Golub et al., 2005b, Islam et al., 2017, Meiring et al., 2018). Improving accessibility to healthcare facilities with TB testing and treatment could include active case-finding, mobile TB clinics and working with the private sectors to ensure adequate support for referring TB patients for appropriate testing. Interventions might also include behavioural change messages, advocacy with community leaders and gatekeepers (Oshi et al., 2020). Improving access to TB care services for women and children need to consider adverse cultural gender and parental norms, especially those that could prevent them from accessing healthcare. Integrating current policies to protect the rights of women and children to access TB care could potentially improve their health protection (Federal Ministry of Health, 2002, Kura and Yero, 2013).

Comparing different sources of data

Findings from the quantitative data were generally in agreement with qualitative findings. Overall, the quantitative findings indicating that males and adults were more likely to progress through the various steps of the cascade, were reflected in the qualitative themes showing parental and spousal influence impacting access to care and disadvantaging women and girls, as well as children. Several studies from Africa, including Nigeria, and Asia have shown similar barriers to TB care for women, children and rural dwellers (Karim et al., 2007, Okeibunor et al., 2007, Tarimo, 2012, Sullivan et al., 2017, Oshi et al., 2016a, Yang et al., 2014, Ibrahim et al., 2014b).

While the data from the 2015 cohort indicated regional differences in access, we were not able to identify major themes related to this, besides the operationalizing of case findings in the different hospital teams, including the use of WhatsApp group messaging. These differences will need to be further explored.

There were differences between the cohort and the cascade of care results, with regards to children. The cohort analysis (Oga-Omenka et al., 2019) showed children were more likely than adults to initiate treatment once diagnosed in the South-West zone, but not at the national-level. One likely reason might be the particular attention given to initiate pediatric patients on treatment once tested within the South-West zone. This earlier treatment initiation in children might not be a complete contradiction as the cascade analysis showed a reduced likelihood of progressing from tested to treatment outcome, and not just treatment initiation alone.

Study strengths and limitations

Using qualitative interviewing permitted an in-depth understanding of the problem of access from the differing perspectives of individuals affected. It is not always the case that the views of patient and their relatives align with those of providers. One strength of this study was that it sought to elicit and compare these different perspectives. In our study, we found that, while health workers mentioned cases where a lack of female autonomy was a barrier to care, female participants themselves did not identify this as a problem. This difference in opinions may have been due to the way the female participants perceived autonomy and cultural norms.

Our study has some limitations. The quantitative data for incidence and access to testing are estimates using routine data. This may have introduced bias into cascade gaps because as estimates, they do not account for the changing patient populations at each stage of the cascade (Subbaraman et al., 2019a). The cohort analysis used in the second step links diagnostic to treatment registers and tracks patients to treatment completion. This may have minimized bias in the cascade estimates at the later stages of the cascade.

Besides 2015, data for the other years used in the cascade estimation and analysis did not show the contribution of the private sector to notifications and treatment numbers. As a large number of Nigerian TB patients seek care first in the private sector, this lack of a clear understanding of the private sector contribution is a limitation of this analysis. If a significant number of people who first present to the private sector are appropriately managed, but not notified to the National TB Program, our estimates at various stages may be overestimated.

There were other limitations due to its qualitative study design (Hodkinson and Hodkinson, 2001). A large amount and range of interview data made analysis complex and impossible to present in its entirety. Also, based on the fact that we conducted interviews in only 2 out of 6 geopolitical zones in Nigeria, the extent to which our results are generalizable to other parts of the country is largely unknown. Additionally, given their status as 'missing', we were unable to seek direct feedback from people who did not present to health centres. Although the perceptions of those receiving care provide insight into the reasons for these gaps, we may have missed potential factors that affect the large proportion of losses at the first stage.

Although participants were further probed and their responses reconfirmed, we cannot exclude the possibility of recall and reporting biases. We addressed this by triangulating sources, location and interview methods. There was an overall consistency in the themes emerging from the different sources of data. Finally, we did not conduct interviews in Northern Nigeria beyond the central geopolitical zone. There is a possibility that particular contexts in these regions were not explored.

Conclusion

Our study has shown that, although there is noticeable progress in access to DR-TB care in Nigeria between 2013 and 2017, this is not nearly enough to meet the End TB targets. On average, less than 3% of estimated incident cases ever make it to treatment completion. This presents serious implications for TB control in Nigeria. Major bottlenecks persist in accessing diagnostic testing and getting diagnosed. Treatment initiation rates also remain sub-optimal.

To reduce gaps in testing and diagnosis, the National TB program needs to make concerted efforts to improve community awareness about symptoms and available resources, private sector engagement and training of providers, and data management, including patient tracking systems.

Gaps in treatment enrolment and completion at the health system level will require increasing access to services and improved coverage, especially for remote locations, as well as policies to protect workers in need of healthcare. The National TB control program also needs to consider specific approaches to address the barriers faced by children and women in accessing services.

References

ABIDI, S., ACHAR, J., NEINO, M. M. A., BANG, D., BENEDETTI, A., BRODE, S., CAMPBELL, J. R., CASAS, E. C., CONRADIE, F. & DRAVNIECE, G. 2020. Standardised shorter regimens versus individualised longer regimens for rifampin-or multidrug-resistant tuberculosis. *European Respiratory Journal,* 55.

AMBE, G., LÖNNROTH, K., DHOLAKIA, Y., COPREAUX, J., ZIGNOL, M., BORREMANS, N. & UPLEKAR, M. 2005. Every provider counts: effect of a comprehensive public-private mix approach for TB control in a large metropolitan area in India. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 562-568.

AWOFESO, N. 2008. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. *Bulletin of the World health Organization,* 86**,** B-D.

BABATUNDE, O. I., BISMARK, E. C., AMAECHI, N. E., GABRIEL, E. I. & OLANIKE, A.-U. R. 2015. Determinants of treatment delays among pulmonary tuberculosis patients in Enugu Metropolis, South-East, Nigeria. *Health,* 7**,** 1506.

COLVIN, C., MUGYABUSO, J., MUNUO, G., LYIMO, J., OREN, E., MKOMWA, Z., MAKAME, M., MWANGOMALE, A., MAHAMBA, V. & MUELLER, L. 2014. Evaluation of community-based interventions to improve TB case detection in a rural district of Tanzania. *Global Health: Science and Practice,* 2**,** 219-225.

DESHMUKH, R. D., DHANDE, D., SACHDEVA, K. S., SREENIVAS, A., KUMAR, A., SATYANARAYANA, S., PARMAR, M., MOONAN, P. K. & LO, T. Q. 2015. Patient and provider reported reasons for lost to follow up in MDRTB treatment: a qualitative study from a drug resistant TB Centre in India. *PLoS One,* 10.

FEDERAL MINISTRY OF HEALTH, N. U. 2002. Women and children rights in Nigeria: A wake up call - Situation assessment and analysis. . *In:* FMOH (ed.). Abuja, Nigeria.

GALE, N. K., HEATH, G., CAMERON, E., RASHID, S. & REDWOOD, S. 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC medical research methodology,* 13**,** 117.

GEHRE, F., OTU, J., KENDALL, L., FORSON, A., KWARA, A., KUDZAWU, S., KEHINDE, A. O., ADEBIYI, O., SALAKO, K. & BALDEH, I. 2016. The emerging threat of pre-extensively drug-resistant tuberculosis in West Africa: preparing for large-scale tuberculosis research and drug resistance surveillance. *BMC medicine,* 14**,** 160.

GIDADO, M., ONAZI, O., OBASANYA, O., CHUKWUEME, N., ONAZI, M., OMONIYI, A. & ODUSOTE, T. 2014. Assessing the Effectiveness of Xpert MTB/RIF in the Diagnoses of TB Among HIV Smear Negative TB Patients in Nigeria. *Journal of Health Science,* 2**,** 145-151.

GLAZIOU, P., SISMANIDIS, C., ZIGNOL, M. & FLOYD, K. 2016. Methods used by WHO to estimate the global burden of TB disease. *Global TB Programme, WHO, Geneva*.

GOLUB, J. E., MOHAN, C., COMSTOCK, G. & CHAISSON, R. E. 2005. Active case finding of tuberculosis: historical perspective and future prospects. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 1183-1203.

GUPTA-WRIGHT, A., TOMLINSON, G. S., RANGAKA, M. X. & FLETCHER, H. A. 2018. World TB Day 2018: The Challenge of Drug Resistant Tuberculosis. *F1000Research,* 7.

HABER, N., PILLAY, D., PORTER, K. & BÄRNIGHAUSEN, T. 2016. Constructing the cascade of HIV care: methods for measurement. *Current Opinion in HIV and AIDS,* 11**,** 102-108.

HASSAN, A., OLUKOLADE, R., OGBUJI, Q., AFOLABI, S., OKWUONYE, L., KUSIMO, O., OSHO, J., OSINOWO, K. & LADIPO, O. 2017. Knowledge about tuberculosis: a precursor to effective TB control—findings from a follow-up national KAP study on tuberculosis among Nigerians. *Tuberculosis research and treatment,* 2017.

HODKINSON, P. & HODKINSON, H. The strengths and limitations of case study research. learning and skills development agency conference at Cambridge, 2001. 5-7.

HONG, Q. N., FÀBREGUES, S., BARTLETT, G., BOARDMAN, F., CARGO, M., DAGENAIS, P., GAGNON, M.-P., GRIFFITHS, F., NICOLAU, B. & O'CATHAIN, A. 2018. The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers. *Education for Information,* 34**,** 285-291.

IBRAHIM, L. M., HADEJIA, I. S., NGUKU, P., DANKOLI, R., WAZIRI, N. E., AKHIMIEN, M. O., OGIRI, S., OYEMAKINDE, A., DALHATU, I. & NWANYANWU, O. 2014. Factors associated with interruption of treatment among Pulmonary Tuberculosis patients in Plateau State, Nigeria. 2011. *Pan African Medical Journal,* 17.

ISLAM, Z., SANIN, K. I. & AHMED, T. 2017. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation research. *BMC public health,* 17**,** 131.

JOMBO, G. & MBAAVE, P. T. 2018. Global Tuberculosis Burden: Is Nigeria Losing The War? *Journal of BioMedical Research and Clinical Practice,* 1**,** ix-xi.

KALIAKBAROVA, G., PAK, S., ZHAKSYLYKOVA, N., RAIMOVA, G., TEMERBEKOVA, B. & HOF, S. 2013. Psychosocial support improves treatment adherence among MDR-TB patients: experience from East Kazakhstan. *The Open Infectious Diseases Journal,* 7.

KARIM, F., ISLAM, M. A., CHOWDHURY, A., JOHANSSON, E. & DIWAN, V. K. 2007. Gender differences in delays in diagnosis and treatment of tuberculosis. *Health policy and planning,* 22**,** 329-334.

KHANAL, S., ELSEY, H., KING, R., BARAL, S. C., BHATTA, B. R. & NEWELL, J. N. 2017. Development of a patient-centred, psychosocial support intervention for multi-drug-resistant tuberculosis (MDR-TB) care in Nepal. *PloS one,* 12.

KURA, S. M. & YERO, B. U. 2013. An analysis of gender inequality and national gender policy in Nigeria. *International Journal of Scientific & Engineering Research,* 4**,** 1-23.

MADHU PAI 2019. Drug-Resistant TB: A Clear And Present Danger. *Forbes.*

MEIRING, C., VAN HELDEN, P. D. & GOOSEN, W. J. 2018. TB control in humans and animals in South Africa: a perspective on problems and successes. *Frontiers in veterinary science,* 5**,** 298.

MERESSA, D., HURTADO, R. M., ANDREWS, J. R., DIRO, E., ABATO, K., DANIEL, T., PRASAD, P., PRASAD, R., FEKADE, B. & TEDLA, Y. 2015. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax,* 70**,** 1181-1188.

NAIDOO, P., VAN NIEKERK, M., DU TOIT, E., BEYERS, N. & LEON, N. 2015. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests. *BMC health services research,* 15**,** 488.

NATIONAL BUREAU OF STATISTICS 2016. DEMOGRAPHIC STATISTICS BULLETIN 2015. Abuja, Nigeria: National Bureau of Statistics Nigeria.

NATIONAL BUREAU OF STATISTICS 2017. DEMOGRAPHIC STATISTICS BULLETIN 2016. Abuja, Nigeria: National Bureau of Statistics Nigeria.

NBLCP/FMOH 2012. First National TB Prevalence Survey Nigeria. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH 2014. The National Strategic Plan for Tuberculosis Control: Towards Universal Access to Prevention, Diagnosis and Treatment- 2015-2020. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH 2015. 2015 Annual Report National Tuberculosis and Leprosy Control Programme. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

OGA-OMENKA, C., TSEJA-AKINRIN, A., SEN, P., MAC-SEING, M., AGBAJE, A., MENZIES, D. & ZAROWSKY, C. 2020. Factors influencing diagnosis and treatment initiation for multidrug-resistant/rifampicin-resistant tuberculosis in six sub-Saharan African countries: a mixed-methods systematic review. *BMJ Global Health,* 5**,** e002280.

OGA-OMENKA, C., ZAROWSKY, C., AGBAJE, A., KUYE, J. & MENZIES, D. 2019. Rates and timeliness of treatment initiation among drug-resistant tuberculosis patients in Nigeria-A retrospective cohort study. *PloS one,* 14**,** e0215542-e0215542.

OKEIBUNOR, J., ONYENEHO, N., CHUKWU, J. & POST, E. 2007. Where do tuberculosis patients go for treatment before reporting to DOTS clinics in southern Nigeria. *Tanzania Journal of Health Research,* 9**,** 94-101.

ONIFADE, D. A., BAYER, A. M., MONTOYA, R., HARO, M., ALVA, J., FRANCO, J., SOSA, R., VALIENTE, B., VALERA, E. & FORD, C. M. 2010. Gender-related factors influencing tuberculosis control in shantytowns: a qualitative study. *BMC Public Health,* 10**,** 381.

ONYEDUM, C. C., ALOBU, I. & UKWAJA, K. N. 2017. Prevalence of drug-resistant tuberculosis in Nigeria: A systematic review and meta-analysis. *PloS one,* 12.

ORGANIZATION, W. H. 2019. Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. *World Health Organization: Geneva, Switzerland*.

OSHI, D., CHUKWU, J., NWAFOR, C., CHUKWU, N. E., MEKA, A. O., ANYIM, M., UKWAJA, K. N., ALOBU, I., EKEKE, N. & OSHI, S. N. 2019. Support and unmet needs of patients undergoing multidrug-resistant tuberculosis (MDR-TB) treatment in southern Nigeria. *The International Journal of Health Planning and Management*.

OSHI, D. C., OSHI, S. N., ALOBU, I. N. & UKWAJA, K. N. 2016. Gender-related factors influencing women's health seeking for tuberculosis care in Ebonyi State, Nigeria. *Journal of biosocial science,* 48**,** 37-50.

SHARMA, N., TANEJA, D., PAGARE, D., SAHA, R., VASHIST, R. & INGLE, G. 2005. The impact of an IEC campaign on tuberculosis awareness and health seeking behaviour in Delhi, India. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 1259-1265.

SHARMA, R., YADAV, R., SHARMA, M., SAINI, V. & KOUSHAL, V. 2014. Quality of life of multi drug resistant tuberculosis patients: a study of north India. *Acta Medica Iranica***,** 448-453.

SUBBARAMAN, R., NATHAVITHARANA, R. R., MAYER, K. H., SATYANARAYANA, S., CHADHA, V. K., ARINAMINPATHY, N. & PAI, M. 2019. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLoS medicine,* 16**,** e1002754.

SULLIVAN, B. J., ESMAILI, B. E. & CUNNINGHAM, C. K. 2017. Barriers to initiating tuberculosis treatment in sub-Saharan Africa: a systematic review focused on children and youth. *Global health action,* 10**,** 1290317.
TARIMO, G. B. 2012. *Delay in seeking care among tuberculosis patients attending tuberculosis clinics in Rungwe district, Tanzania.* Muhimbili University of Health and Allied Sciences.
THOMAS, B. E., SHANMUGAM, P., MALAISAMY, M., OVUNG, S., SURESH, C., SUBBARAMAN, R., ADINARAYANAN, S. & NAGARAJAN, K. 2016. Psycho-socio-economic issues challenging multidrug resistant tuberculosis patients: a systematic review. *PloS one,* 11.
TOPE, A. T. 2014. Can Nigeria Sustain the Fight against Drug Resistant Mycobacterium tuberculosis? *Journal of Microbiology Research,* 4**,** 72-77.
WORLD HEALTH ORGANIZATION 2014. *Global tuberculosis report 2014*, World Health Organization.
WORLD HEALTH ORGANIZATION 2015. *Global tuberculosis report 2015*, World Health Organization.
WORLD HEALTH ORGANIZATION 2016. Global tuberculosis report 2016.
WORLD HEALTH ORGANIZATION 2017. *Global tuberculosis report 2017*, World Health Organization.
WORLD HEALTH ORGANIZATION 2018. *Global tuberculosis report 2018*, World Health Organization.
WORLD HEALTH ORGANIZATION 2019a. Global tuberculosis report 2019.
WORLD HEALTH ORGANIZATION 2019b. No Time to Wait: Securing the future from drug-resistant infections
- Report to the Secretary-General of the United Nations.
YADAV, S. K., DAMOR, R., KANTHARIA, S. & TIWARI, M. 2015. Assessment of Knowledge and Treatment Seeking Behaviour among Tuberculosis and Multi-Drug Resistant Tuberculosis Patients:-A Case Control Study. *IOSR Journal of Dental and Medical Sciences,* 14**,** 66-71.
YANG, W.-T., GOUNDER, C. R., AKANDE, T., DE NEVE, J.-W., MCINTIRE, K. N., CHANDRASEKHAR, A., DE LIMA PEREIRA, A., GUMMADI, N., SAMANTA, S. & GUPTA, A. 2014. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberculosis research and treatment,* 2014.
YASSIN, M. A., DATIKO, D. G., TULLOCH, O., MARKOS, P., ASCHALEW, M., SHARGIE, E. B., DANGISSO, M. H., KOMATSU, R., SAHU, S. & BLOK, L. 2013. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. *PloS one,* 8.

Supplementary File – Article 4

The DR-TB care cascade and process indicators

4A The DR-TB care cascade and process indicators

Cascade stage	Outcome indicators for cascade steps	Methods or required data for outcome indicators	2013 Cases [Range]	2014 Cases [Range]	2015 Cases [Range]	2016 Cases [Range]	2017 Cases [Range]	Process indicators used	Methods used for process indicators
Stage 1: Reaching health facilities and accessing a TB test	**Step 1: Number of individuals with incident or prevalent DR-TB in the population**							**Gap 1: Number of individuals with TB who did not reach health facilities and access a TB diagnostic test**	
	Annual number of individuals with incident active TB in a population for all forms of TB	Population-based TB prevalence survey (2012) WHO TB Burden Estimate using prevalence surveys, notification data, national inventory studies and expert opinion on case detection gaps	590,000 [340,000-880,000]	570,000 [340,000-870,000]	586,000 [345,000-890,000]	407,000 [266,000-579,000]	418,000 [273,000-594,000]		
	Estimated number of individuals with DR-TB	Incidence of RIF-R cases in the annual tuberculosis burden	**17,100** [9,900-25,500]	**16,500** [9,900-25,200]	**29,000** [15,000-43,000]	**20,000** [12,000-29,000]	**24,000** [14,000-36,000]	Time delays in care seeking Individuals who died of TB without having received DR-TB care	Qualitative interviews with individuals starting DR-TB treatment at health facilities and communities Qualitative interviews with families of individuals who died of probable DR-TB Qualitative interviews with providers of DR-TB care at the health center and community levels
Stage 2: Diagnosis	**Step 2: Number of individuals with DR-TB who reached health facilities and accessed a TB diagnostic test**							**Gap 2: Number of individuals with TB who accessed a TB diagnostic test but did not get successfully diagnosed**	
	Number of individuals with DR- TB who accessed TB tests	Extrapolation from WHO TB burden estimating the proportion of DR-TB among new and previously treated patients among notified pulmonary TB cases (4.3% [3.2-5.4] of new cases, 25% [19-31] of previously treated)	**3,700** [2,800-4,600]	**3,300** [2,500-4,200]	**4700** [3700-5700]	**5200** [4100-6200]	**5400** [4200-6500]	Health system–related delays in diagnosis	In-depth interviews with patients starting DR-TB treatment and their supporters Qualitative interviews with providers of DR-TB diagnosis and treatment at the health center and community levels

Stage 3: Linkage to treatment	**Step 3: Number of individuals diagnosed with DR-TB**							**Gap 3: Number of individuals diagnosed with TB who did not get registered in treatment**	
	Number of individuals with DR TB who were successfully diagnosed as having drug-resistant TB	Identified through National Gene Xpert register (GX Alert)	**669**	**798**	**996**	**1691**	**2300**	Delays in treatment initiation	In-depth interviews with patients starting DR-TB treatment and their supporters Qualitative interviews with providers of DR-TB diagnosis and treatment at the health center and community levels
Stage 4: Retention in treatment	**Step 4: Number of individuals registered in DR-TB treatment**							**Gap 4: Number of individuals who did not complete TB treatment (due to treatment failure, loss to follow-up, or death)**	
	Number of individuals registered on DR-TB treatment	TB electronic DR-TB treatment register (e-TB Manager)	**339**	**423**	**660**	**1255**	**1796**	Proportion of and reasons for patients who die, or are lost to follow-up in the intensive and continuation phases of therapy	TB treatment records In-depth interviews with patients on DR-TB treatment and their supporters Qualitative interviews with providers of DR-TB diagnosis and treatment at the health center and community levels
Stage 5: Post-treatment survival	**Step 5: Number of individuals who completed DR-TB treatment**							**Gap 5: Number of individuals who experienced post-treatment TB recurrence or death**	
	Number of patients who complete TB therapy	TB electronic DR-TB treatment register (e-TB Manager)	**261**	**313**	**511**	**963**	**N/A**		

Article 5: Ease and Equity of DR-TB Care Access

Title page

Title: Ease and equity of access to free DR-TB services in Nigeria- a qualitative analysis of policies, structures and processes

Charity Oga-Omenka[1,2,3], Florence Bada[4], Aderonke Agbaje[4], Patrick Dakum [4], Dick Menzies[3,5], Christina Zarowsky[1,2,6]

1. The School of Public Health of the University of Montreal (ÉSPUM), Montreal, Quebec, Canada
2. Centre de recherche en santé publique, Université de Montréal (CReSP), Canada
3. McGill University International TB Centre, Montreal, Quebec, Canada
4. International Research Center of Excellence, Institute of Human Virology Nigeria
5. Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada
6. School of Public Health, University of the Western Cape, South Africa

Corresponding author: Charity Omenka

Funding:

COO received funding for fieldwork through the Global Fund New Funding Model MDR TB Grant (Global Fund to Fight AIDS, Tuberculosis and Malaria: NFM MDR TB Grant), with funds provided through IHVN as the Principal Recipient. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Status: This article has been provisionally accepted for publication pending revisions with the International Journal of Equity in Health. Reviewers' comments have been addressed but not yet reviewed with co-authors.

DOI: https://www.researchsquare.com/article/rs-39365/v1

Abstract

Introduction:

Persistent low rates of case notification and treatment coverage reflect that accessing diagnosis and treatment for drug-resistant tuberculosis (DR-TB) in Nigeria remains a challenge, even though it is provided free of charge to patients. Equity in health access requires availability of comparable, appropriate services to all, based on needs, and irrespective of socio-demographic characteristics. Our study aimed to identify the reasons for Nigeria's low rates of case-finding and treatment for DR-TB. To achieve this, we analyzed elements that facilitate or hinder equitable access for different groups of patients within the current health system to support DR-TB management in Nigeria.

Methods:

We conducted documentary review of guidelines and workers manuals, as well as 57 qualitative interviews, including 10 focus group discussions, with a total of 127 participants, in Nigeria. Between August and November 2017, we interviewed patients who were on treatment, their treatment supporter, and providers in Ogun and Plateau States, as well as program managers in Benue and Abuja. We adapted and used Levesque's patient-centered access to care framework to analyze DR-TB policy documents and interview data.

Results:

Thematic analysis revealed inequitable access to DR-TB care for some patient socio-demographic groups. While patients were mostly treated equally at the facility level, some patients experienced more difficulty accessing care based on their gender, age, occupation, educational level and religion. Health system factors including positive provider attitudes and financial support provided to the patients facilitated equity and ease of access. However, limited coverage and the absence of patients' access rights protection and considerations in the treatment guidelines and workers manuals likely hampered access.

Conclusion:

In the context of Nigeria's low case-finding and treatment coverage, applying an equity of access framework was necessary to highlight gaps in care. Differing social contexts of patients adversely affected their access to DR-TB care. We identified several strengths in DR-TB care delivery, including the current financial support that should be sustained. Our findings highlight the need for government's commitment and continued interventions.

Introduction

Nigeria has overlapping high burdens of tuberculosis (TB), drug resistant tuberculosis (DR-TB) and HIV, according to the World Health Organisation (WHO) (WHO, 2019a). However, in 2018, the country of 198 million people had one of the lowest global TB case detection rates at 24%. Only about 11% and 9% of estimated DR-TB cases were notified and initiated on treatment, respectively (WHO, 2019a). This highlights major difficulties in accessing DR-TB care (WHO, 2019a). The country has identified finding the missing TB cases as the single most important priority for TB control for the upcoming years, as each untreated case can infect 15-20 persons per year (NBLCP/FMOH., 2019).

In terms of health financing, Nigeria spent 3.76% of gross domestic product (GDP) in 2017 (The World Bank, 2016). With a per capita GDP of USD 5,864, 8% and 32% of the TB budget was domestic and donor funded respectively. This leaves 60% of the National TB budget required to implement the Stop TB Partnership's Global Plan to End TB 2018–2022 unfunded (WHO, 2019a, The World Bank, 2016, International Monetary Fund, 2019) . Seventy-one percent of TB patients faced catastrophic health costs in 2017 (WHO, 2019a).

South Africa and Zimbabwe are two examples of countries also classified as high burden for TB, DR-TB and HIV in Africa. In 2017, South Africa spent 8.1% of its $13,396 GDP (PPP) on health and funded 87% of TB budget internally, with 0% unfunded. The country had 100% and 87% DR-TB notification and treatment rates in 2018. Comparatively, Zimbabwe spent 6.6% of $2,782 GDP (PPP) on health and domestically funded only 1% of TB budget; with 31% donor funding, leaving 69% unfunded. Despite this, Zimbabwe had 27% and 25% DR-TB notification and treatment rates (WHO, 2019a, The World Bank, 2016, International Monetary Fund, 2019). These suggest other barriers to TB care in Nigeria, in addition to health financing.

Equitable health systems ensure services are available to everyone in need (Levy and Sidel, 2013, Goddard and Smith, 2001, Gwatkin et al., 2004, Kruk and Freedman, 2008, Braveman, 2003). Policy experts have proposed that governments particularly evaluate health systems through their impact on the poor, in order to reverse the inequities in delivery (Kruk and

Freedman, 2008, Braveman, 2003). In the TB context, several authors including the WHO, have highlighted the need to target specific sociodemographic groups identified as being at a higher risk of contracting the disease or of having poorer access or outcomes, once infected (Gwatkin et al., 2004, Andrews et al., 2015). Another aspect relevant to an equity analysis is the complexity of the TB care pathways- the number of patient visits and pre-treatment processes needed in order to achieve an outcome.

Equity and ease are two ways of looking at access to healthcare. Equity of access focuses on the health system, or supply-side, to ensure equal services for patients in equal need (Raine et al., 2016). Ease of access explores individual and societal barriers to available healthcare services (Raine et al., 2016, Levesque et al., 2013). Effective and equitable access combines these two aspects: the ability to obtain timely health services based on needs, irrespective of sociodemographic characteristics, and without risking financial hardship (Almgren, 2018, Gulliford et al., 2002, Evans et al., 2013, Levesque et al., 2013). Both are important access indicators to monitor the performance of healthcare systems (Rubenstein et al., 2020, Argy, 1996, Gulliford et al., 2002). These definitions are in line with the Levesque et al. characterisation of access as having two main domains (Levesque et al., 2013).

This study aimed to explore patient-centered ease and equity of access to diagnosis and treatment initiation for DR-TB patients through an analysis of policies, structures and processes for DR-TB care in Nigeria.

Methodology

We used a transformative study design using key informant interviews, focus group interviews, and document review. This is part of a larger mixed methods cascade study, with previously published quantitative results and a mixed methods cascade paper (Oga-Omenka et al., 2019, Oga-Omenka et al., 2020b). In this paper, we report qualitative data for an additional research question. This builds on the factors influencing the identified gaps in the cascade paper (Oga-Omenka et al., 2020b) by exploring the equity of health systems as they relate to the ease with of access to care for patients. We used a transformative design which involves a theoretical lens to guide interpretation and advocate for action (Creswell et al., 2003, Mertens, 2007).

Transformative research advocates for social justice and addresses power imbalances, by focusing on inequalities and marginalization, and this is reflected in every stage of the research (Mertens, 2007, Sweetman et al., 2010). We focused on understanding the perspectives and experiences of patients, including those not on treatment, their relatives, care providers and program managers, through an equity of healthcare access framework. Our framework, adapted from the work of several authors (Levesque et al., 2013, Yang et al., 2014, World Health Organization, 2010), helped to identify inequities within the supply and demand sides of access, and highlight areas for improvement.

Conceptual framework

The predominant theoretical framework guiding our transformative study is the Levesque patient-centred access to healthcare framework (Goddard and Smith, 2001, Levy and Sidel, 2013, Levesque et al., 2013). This was also considered through the lens of the TB continuum of care (Yang et al., 2014, Subbaraman et al., 2019b), and the WHO's health system building blocks (WHO, 2010b). Our adapted framework (*figure 18*) was used to frame our qualitative instruments and to interpret findings.

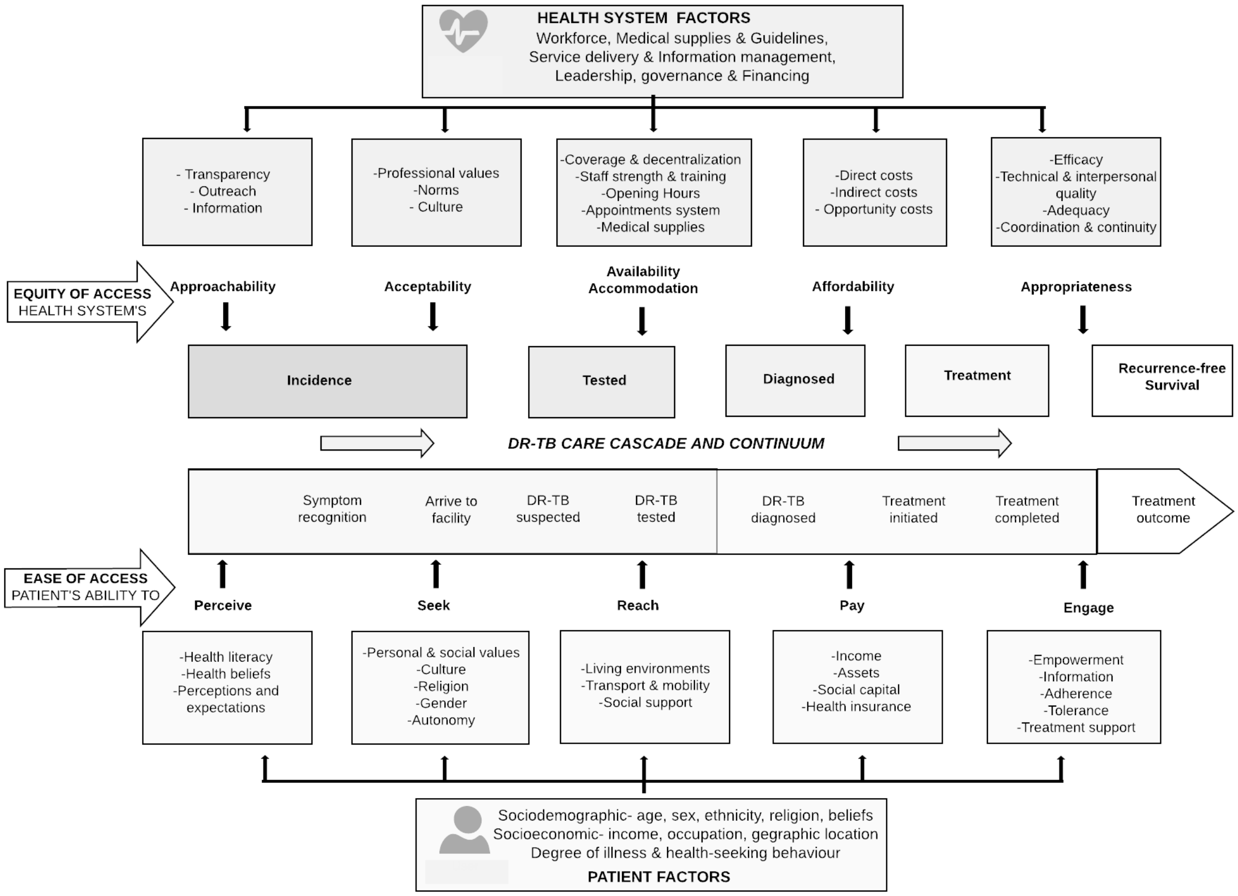


Figure 18. – An adapted framework of equity and ease of access to DR-TB care

At its core, the Levesque framework conceptualizes accessibility in five dimensions: approachability, acceptability, availability, affordability, and appropriateness of providers, organizations, institutions and systems. These dimensions must be matched with five corresponding abilities in patients for patients and communities: ability to perceive (or identify needs), seek services, reach resources, pay, and engage, respectively (Levesque et al., 2013).

These healthcare and patient dimensions should be progressive as the patient moves from one stage of the care continuum to the other.

Study population and data collection

We reviewed several National TB and Leprosy Control Program (NTBLCP) and Federal Ministry of Health (FMOH) policy and guideline documents using content analysis, as well as annual reports on DR-TB care in Nigeria between 2015 and 2017, some unpublished (FMOH, 2008, NTBLCP, 2017a, NTBLCP, 2010, NTBLCP, 2017b, Institute of Human Virology Nigeria, 2017, NBLCP/FMOH., 2015, NBLCP/FMOH., 2019). These included the TB HIV treatment guideline, workers' manuals, annual TB reports and WHO country profiles.

This is part of a larger mixed methods study, with previously published quantitative results (Oga-Omenka et al., 2019). We analysed data from 57 interviews. These included focus group discussions (FGDs) (n=10) with a total of 81 patients on treatment, treatment supporters and community members; as well as 46 in-depth interviews with untreated patients, healthcare providers and program managers. Interviews covered 4 locations within Ogun, Plateau, and Benue states and Abuja, Nigeria, between August and November 2017. Our sampling frame is shown in Figure 19.

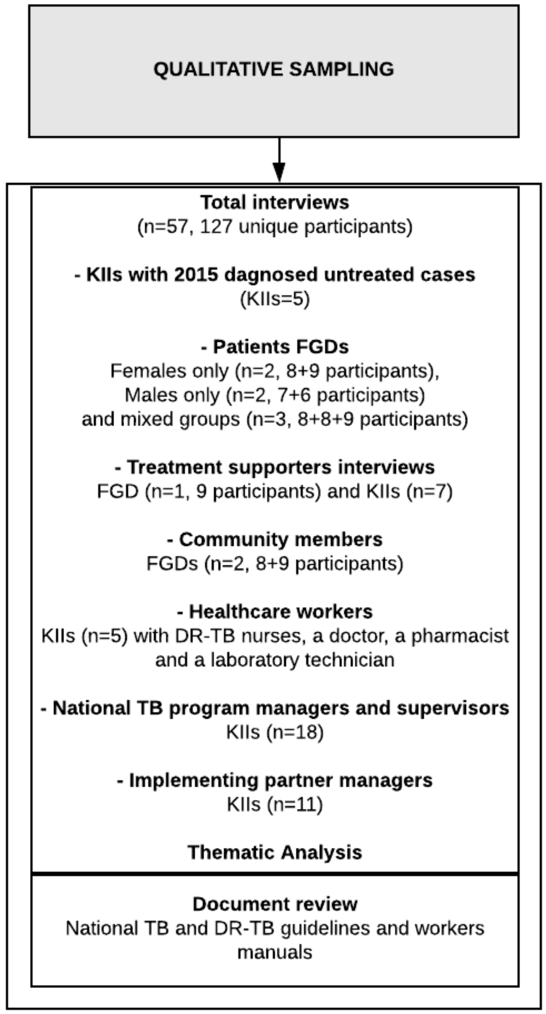


Figure 19. – Qualitative sampling

Our overall sampling strategy was purposive, selecting participants whose views would most likely be information-rich about delays in DR-TB care, as described above. Within this sampling approach, we selected participants based on availability and consent. We triangulated sampling methods - combining purposive, negative case and convenience sampling.

Healthcare workers' questions included program structure, challenges and strengths, as well as their perception of access barriers and facilitators. Patients and their treatment supporters were also asked to describe barriers and facilitators to accessing DR-TB care that they, their relative or someone they knew had experienced. Female and male only FGDs were additionally probed for any particular challenges facing their gender in accessing care. In addition to the questions for healthcare workers, program managers and implementing partner respondents were asked about the available resources at the national, regional and state level for DR-TB care, their perspectives on the adequacy of these resources, and relevant policy documents on DR-TB care. The documents and guides recommended by respondents were also included in the analysis.

Informed consent from each participant were written or verbal (where needed), before each interview. The first author, who had prior DR-TB implementation experience in Nigeria, carried out the interviews with help from a field assistant. All interviews were conducted in English. However, some questions were translated into Nigerian pidgin, Yoruba or Hausa, if any participant requested it, using local translators. Interviews were audio-recorded, translated where needed and transcribed. Where portions of the transcripts included translations and responses in the other languages, a transcriber fluent in this language was used. We conducted member checking as a way to strengthen the rigour of our study (Krefting, 1991). Transcripts were sent back to all participants who had earlier agreed to be contacted for accuracy checking, some of whom responded with revised transcripts which we used to replace the original transcripts.

Data analysis

Data analysis began during data collection to enable exploration and comparisons of new themes. Our interview guide, which was based on initial literature review and our conceptual framework, was used to deductively develop a coding tree before the process of coding began. Transcripts were checked and read through to give a general understanding of the data. The first phase of coding was inductive to allow new themes to be added to the coding tree. Codes were then deductively matched to the coding tree, with a few new codes added as needed. Coding of documents and interview transcripts were around themes based on our conceptual framework of Equity of access to DR-TB care (*figure 18*). The thematic analysis focused on how the system facilitates patient progression after arrival with symptoms at the TB clinic to the point of treatment initiation, as well as on patient pathways to care.

Document analysis helped to triangulate evidence from the in-depth interviews. This also facilitated member checks (participant feedback on emerging themes) to ensure fidelity with participant intents as recommended by Seale (Seale, 1999). Data analysis was facilitated by the use of the Quirkos software, version 1.6.1. Our findings are reported according to the consolidated criteria for reporting qualitative studies (COREQ) (Tong et al., 2007)

Ethics

The National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007) and the Research Ethics Committee (CER) of the University of Montreal Hospital (17.060) granted ethical approval for this study An additional ethical approval was obtained from the Research Ethics Committee (CER) of sciences and health of the University of Montreal (CERSES-19-098-D). All participants gave written or verbal informed consent.

Results

Our findings focus on the outputs needed from the health system and the patient to achieve DR-TB cure, by looking at required supply and demand dimensions and how they align with each step in the care continuum, starting from symptom recognition, through health-seeking to completing treatment (Roscoe et al., 2020). The five paired supply and demand dimensions, based on the Levesque framework, are presented below and summarised in the *figure 20*.

	Approachability	Acceptability	Availability and accommodation	Affordability	Appropriateness
EQUITY OF ACCESS	- Lack of individual and community awareness on the symptoms of TB and availability and location of free care - Inadequate structure and quantity of outreach services - TB services not as approachable as traditional healers, patent medicine vendors or pharmacies - Low index of suspicion in private health facilities	- Poor referral system between private and public health facilities - Inadequate engagement and oversight of public-private partnerships especially with faith-based organizations and traditional healers - Patients cited poor perception due to public sector poor provider attitudes, unsanitary conditions, lack of essential medical supplies and accountability	- Inadequate coverage of testing (48%); mostly public tertiary and secondary facilities - Inadequate coverage of treatment (27 out 0f 37 states); mostly public tertiary and secondary facilities - Operational delays - Inadequate staff numbers and quality - Data errors affecting patient tracking and follow-up	- High pre-treatment costs for laboratory investigations - Lengthy pre-treatment procedures contribute to costs - Program patient financial support a major treatment enabler -	- Poor referral system between private and public health facilities - Inadequate engagement and oversight of public-private partnerships especially with faith-based organizations and traditional healers
	Ability to perceive	**Ability to seek**	**Ability to reach**	**Ability to pay**	**Ability to engage**
EASE OF ACCESS	- Respondents recommend TB health education on TV and radio to maximise reach - Respondents recommend that the TB program engages former pateints as community advocates	- Negative perception of public health facilities - Belief that a quicker solution can be found with alternative care - Attributing disease to spiritual causes - Patient's lack of autonomy in making health decisions especially for children and women, hampered access	- Poor transport network - Hard-to-reach geographical locations far from higher level public facilities - Impatience with lengthy pre-treatment processes and operational delays - Work, school and family commitments sometimes a barrier to care	- High costs of wrong diagnosis and treatment often in private sector -High costs of pre-treatment investigations - Transport costs for return appointments prohibitive	- Toxicity of second line drugs a barrier to care for many patients - Reported cases of patients forced out of care by family members - Attributing disease to spiritual causes

Figure 20. – Ease and equity of access to free DR-TB care in Nigeria

Approachability and ability to perceive

Certain attributes of the healthcare system and of patients align when the patient recognizes that observed symptoms require medical attention and that certain health services can be accessed. The health system enables this through patient education, transparency and outreach services information (Levesque et al., 2013). This stage in the care continuum should end with the patient deciding to seek care for their health problem.

The national guidelines stressed the need for patient education and community awareness and outreach activities (FMOH, 2008, NTBLCP, 2017a). Routine patient education is to include cause and symptoms of TB, availability and free cost of treatment, where to seek healthcare, and how to prevent spread. These activities are to be implemented through home-based care for HIV and TB patients (FMOH, 2008). The guidelines encourage healthcare workers to conduct campaigns and sensitization activities to increase testing requests, actively search for cases within the health centers especially for HIV patients, sensitize providers and engage community-based organizations (NTBLCP, 2017a, NTBLCP, 2010). However, the guidelines are not immediately clear about the frequency or funding provisions for these campaigns. It also does not say how active case-finding in the community should be done, although several implementing partners are tasked with these activities.

Patients, their relatives and providers agreed that there was limited awareness about DR-TB in the communities.

“The point is, not everybody knows about TB…I didn't actually have the full knowledge of what TB was, so when I got infected, that was when I knew. Ah, this thing is really serious! But… people out there, I don't think the information has been passed enough to people, especially those in the rural areas...they just feel it is this strong cough that doesn't go away. [A herbalist] prescribes herbs for [them] to take and they think okay, it is just a normal cough that will [go away]....I think the awareness [is important] because when someone is aware [of] what is at stake…[they] will be …like... okay, this is [serious]...lets go to the hospital” Mixed patients FGD.

This often resulted in prolonged pathways to DR-TB care, because DR-TB care were most often available in the public sector. These delays ran into several months to a couple of years, in many cases. Patients acknowledged that the private sector, including patent medicine vendors (PMVs), community pharmacies and private hospitals, were the first point of contact with healthcare but that private practitioners had lower index of suspicion for DR-TB. The annual TB reports also showed much lower coverage of free DR-TB services in the private sector, limiting the approachability of public healthcare (NBLCP/FMOH., 2015, NBLCP/FMOH., 2019).

“So, I [didn’t] really know what to do [anymore] I was … given the herbal [preparation], I went to church, I went to mosque, went to everywhere, but all [remained] the same I won’t lie to you, [DR-TB] is very strong and very powerful…because I can tell you so many drugs that I have used, I have used ampicillin for about two to three years; [a lot of it] for about two to three years it will just relieve me and then it will come back, that is, it will come back” (Diagnosed untreated male patient).

Respondents mentioned that being told by a healthcare worker in the community, or by a former TB patient, helped them to realise their symptoms were treatable for free in the hospital. Healthcare workers were frustrated that there was more knowledge about HIV in their communities than of TB.

Government TB control officers and program managers mentioned that outreach activities have increased case finding in the communities they supervise.

*"So, somebody who would have stayed at home using traditional medicine, thinking that this is just an ordinary cough … but with the outreaches, [any] cough of 2 weeks… please come out for testing, and from the outreaches a lot of cases have been identified" (*Male program manager).

Acceptability and ability to seek

For a patient to utilize healthcare, the health services need to have a higher perceived benefit than other options available to the patient, as well as not to violate any cultural, religious or social norms the patient has. This stage is also affected by the health systems professional values, culture and norms, as well as the patient's autonomy (Levesque et al., 2013). This stage ends with the patient choosing a particular source or type of care over other options.

As part of the TB private-public partnership strategy, the TB program worker's manual included notes to organize regular meetings with relevant stakeholders including PMVs and traditional healers at state levels, with national oversight (NTBLCP, 2010). Monitoring meetings with community-based organizations were also to include religious bodies (NTBLCP, 2010). It was not clear from our data how often and where these activities were happening.

Patients, relatives and providers gave several narratives of patients visiting multiple sources of alternative care in search of a cure like PMVs, traditional healers and prayer houses, and most often before ever going to a health center. Sometimes, this was due to being unaware of DR-TB services, inconvenience of these services, misdiagnosis in a private hospital or family influence on patients' autonomy.

"I have not really seen many [cases like this] …except for a case of a student I saw when I went for on a supervisory visit … this student … was diagnosed with TB but his mum did not believe that he had TB. His mum felt that it was a spiritual issue that should be [handled] with prayers. I took up the phone and called her and despite all my pleading and explanation, [and even though] she said ok she was going to bring her son the next day, … she never came. …. This is one clear example of where a parent of a … minor prevented the child from having access to care" TB Program Manager Interview.

The documents we reviewed did not mention protecting the right to health for minors, marginalized groups or other persons who might not be able to take a health decision on their own.

Other times, it was because the patients had more confidence in alternative healers than in the public sector hospital or wrongly attributed TB to other causes. As one HCW puts it:

"*I've treated one educated person here, [not] until he started the drug and [in] the second month [when] he [could] see the difference that … he believed truly TB is a disease. [Before then], he believed somebody [evil was harming] him; [imagine that] an educated [person]! So I [had] to make copies of … our National [training guides], to give to him, to go and read, that TB is just a normal thing [it is not supernatural]; and that you [can] be infected [anywhere], … from an infected person*" HCW interview.

Patients reported that they preferred to go to private hospitals because of widespread perception of better provider attitudes. The major acceptability barriers to public hospitals included poor provider attitude, unsanitary conditions, and lack of essential medical supplies and accountability.

"Most of private hospital they don't know [the right thing to do], and private hospital is where most people go to. [Government should] first … do something [about] private hospitals because … people will think [they] are getting [good treatment], whereas it is just [the wrong medication] … In this country, if something happens, people … go to private hospitals, and they should. [Government hospitals] don't treat people well. I can't give birth in a government hospital , my younger one was dying in a government hospital and they said it is not their business, if you don't

get a particular [item], if you don't get [say, a facemask], they will not attend to [your] child, before we could get [the facemask], the child had died. Government hospitals treat people like dogs, like animals, like …whatever happens to you is not their business, they will [still] get paid. In private hospitals, they will be sweeping and cleaning every minute …, and telling you sorry every time, [and] you … feel a little bit consoled" (Female patients FGD 1).

Patients were more inclined to use the public sector on the recommendation of someone in their community that they trusted, like their pastor or family member. Interviews with members of the community also highlighted the effect of community awareness campaigns in changing people's beliefs about health services.

Availability, accommodation and ability to reach

For patients to be able to reach a health service, it needs to be geographically available, with accessible opening hours and appointment systems. The patient should have access to secure transport to reach these services. At the health facility, the patient needs to come in contact with a knowledgeable provider who suspects and tests for DR-TB. This would also need to align with the patient's support system. At the end of this cascade stage, the patient should be known to the health system and recorded as "tested".

Based on the annual TB program reports from 2015 to 2017, coverage in services was scaled up nationally: testing facilities increased from 201 to 386 (testing), in-patient treatment centres from 13 to 29 and community outpatient treatment centres from 5 to 200 (Gidado et al., 2019, NBLCP/FMOH., 2015, NTBLCP, 2017b). Most of the testing facilities were located in the tertiary and secondary public health centres, with only13% and 6% of testing in the private sector and primary health care level respectively (Gidado et al., 2019). In-patient treatment centres were in 27 out of 37 states, and all were in tertiary or secondary facilities, with 17% in private hospitals, excluding patients who were initiated on treatment in the communities. Geographic coverage of testing was 48% at the end of 2017 (Gidado et al., 2019).

Respondents mentioned the lack of testing and treatment facilities near them as a barrier. Many patients lived far from the health facility, with transportation difficulties, especially in rural areas.

“Some people do not have the opportunity to come down to this place; if it is in their State they will also be able to go to the clinic close to them to [test], knowing that when they get there they will [be treated] well" (Female patients FGD 1).

Several health system barriers were noted including clinic and laboratory operational delays, data errors and stock-outs of essential health products. Healthcare workers gave instances of patients giving wrong contact information, due to poor confidence in the public healthcare system, which affected patient tracking and resulted in loss to follow-up. The treatment guidelines and workers manuals we looked at did not include any procedure for address verification for patients being tested or initiated on treatment.

Healthcare workers also noted limited staff numbers as a major challenge.

"... because we don’t have manpower on ground. … In a particular facility probably, they are only two [staff] and in some cases there is only one personnel. Now you will be handling this, … you will be doing this [and that]. So, at the end you may not even have time for some of your patients ... that is the greatest challenge we have" (Female HCW)

Affordability and ability to pay

The direct and indirect costs of accessing care and the patient’s socioeconomic situation determine whether a patient gets diagnosed and placed on treatment. These costs and ability to keep paying for them will determine if the patient initiates and continues on treatment.

Patients narrated facing catastrophic treatment costs, mostly in the private sector, before finding the right health center for DR-TB care. Other direct and indirect costs were related to transportation for follow-up appointments and for pre-treatment investigations.

However, with support from partners, the TB program pays transport and social support to patients enrolled on treatment, at approximately USD100 per month (Institute of Human Virology Nigeria, 2017). Patients repeatedly mentioned that the financial support was the biggest facilitator of access for them and their loved ones.

"If not for [the program], many people would have died, because of [DR-TB]. Because it is too costly to handle personally, we just thank God for the people that brought this program because it is very, very expensive to manage. I'm the happiest woman … here, because when I remember [what I went through with] my daughter, how [we moved] from [one hospital to another]. [A simple] razor blade, before [any hospital staff] will give you that razor blade, you [will need to] go and pay in to the [hospital] account … I thank God for [the program]. They make me to be the happiest woman on this earth because [I would have lost my 15-year-old] child … but today they put laughter into my own family. ... Thank you." (Treatment supporters FGD).

Appropriateness and ability to engage

The healthcare system also needs to be efficacious, well-coordinated, uninterrupted and support the patient to be empowered and adhere to the treatment regimen to its completion. The patient also needs to be able to tolerate or withstand the effects of treatment and have adequate support from their social network. Only then can the desired treatment outcome be achieved.

There were instances of patients losing hope during the long duration of treatment or having unbearable side effects, including pain from injections, to the point where the possibility of dying was preferable to remaining on treatment.

"[An elderly man], …when he sees the tray for drugs, … he will start vomiting, ha! even when they have not given him, as soon as he sees it, he starts vomiting. At last even nurse or doctor, when he sees them he will just start vomiting, and finally he said he wants to go, … if he even sees the color of the doctors or nurses uniform he will be so afraid…he said it is better for him to go and die… maybe he is dead but we don't know, but if he just sees them even there is no drugs he will start vomiting. .. they gave him paper to sign out of treatment…and he signed out and left because he [couldn't] bear the pain [anymore]" (Female patients FGD 2).

"*We have some that after starting treatment, due to adverse drug reaction you know, some of them may tell you that I better die than to be taking this drug*" HCW interview.

In several cases, having a caring healthcare worker made the difference between continuing treatment or not.

"*Taking the drugs, to be frank, is very difficult. When you take the drugs, you will feel serious pain. Sometimes some people will be shouting, shouting; … the injection is like that. …sometimes we are together with the nurses while the injection is being given, and during that period, you will be see different people shouting, shouting because of the injection, some people will even be running from the injection. To be frank the nurses are very caring. and God will bless them all for their effort*" Female Patients FGD.

"*After some months, I saw the next [medication], I refused because the pain [I was] going through. So, I didn't want to take the treatment, but the way [the HCWs] talked, pleaded. When they came, they started pleading with me… That's why I … decided, let [me just] go ahead and take it*" Mixed Patients FGD.

Healthcare workers cited a few instances of patients whose families prevented their treatment completion because of their own beliefs that the private sector will offer a cure.

At the health system level, several barriers were noted, including stock out of essential supplies, and inadequate patient counseling.

Overview of equity and ease of access to free DR-TB services

Our document review found, and providers and the patients affirmed, that the DR-TB program provided financial support for patients on treatment, which patients acknowledged as the main facilitator to access.

"*The day they gave me the result and said it was TB, I was like ah! And I started thinking that where do I … get money [for treatment]. I told my husband and he was worried. The doctor then said that whatever we are using here will be free of charge. I was like, it a lie, there is no how I will come here and will not spend money. I wanted to drop the money on me. They were like, no, I should go [home] with it.... When we got to where we will do [the] X-ray, I was like, how much am*

I spending? They said I am not spending anything, that I should go home, because everything they do here is free." Patients FGD.

There were very many instances of healthcare workers personally going well beyond their professional duties to help patients remain in care.

"*We pay nothing. Even when I go to hospital without money, the person giving us drug [would] give me money for transport from her personal purse and I keep thanking her till today because she really took good care of me*" Patients FGD.

However, to be placed on treatment, there were significant challenges with coverage of services, prolonged care processes, operational errors and provider attitudes.

"When I got to that general hospital to do test …, which [was 6 months ago] they said …am going to do eight tests, am going to do seven there [at the general hospital] then the other one at [another location]. [eventually], I did everything, I have [done] the … seventh test at general [hospital]… so it is remaining, one, at [the other location], they said that one … audiometric or (hiss) I have forgotten what the doctor called it.… which is the eight one. …[I just did], the x-ray. Everything -the results- are still at home" (Untreated male patient).

All groups of respondents mentioned that some groups of patients had more difficulty accessing care. These include patients living in rural communities far from TB healthcare centres, children whose parents had low trust or information about public healthcare, patients in the private sector, women due to adverse cultural norms that necessitated asking for their husbands' permission to access care, workers and students.

These difficulties are reflected in the following quotes:

"A 12 years old [girl] came down with … resistance and the mother vehemently refuse to take her for treatment all in the name of she has given her some cough syrup. The state team went there … yet this woman stood her ground that she will not allow the daughter to leave … The TBLS (TB Local Government Supervisor) …the woman took one knife at… him … So, now the small [child]

that is bearing the pain. But because she is small, she can't take decision on her own." (Male program manager).

Livelihoods and education were threatened or interrupted, even for patients' relatives, in order to navigate the process of care.

"*I was learning before, I should have finished learning this year before this TB stopped my learning. It was remaining 4 months for me to complete*" (Female patient relative).

"The reason why I don't want to start now is that…is work! My work…And my house rent is going to be due in November which is next two months;… the reason why I don't want to [go for treatment] now, is that if the house rent should be due [how can] I tell my landlord that I am leaving for the hospital?! ...I am going to pay for the house rent" (Untreated male patient).

Overall, there was cohesiveness between data source (document versus interviews) and respondent type. However, there were a couple of differences. For example, while the national guidelines recommended that community awareness be carried out, it was not very clear how these were to be funded or implemented by the healthcare worker. Also, several healthcare workers cited cases of female patients and children being prevented from accessing care because of an authority figure, participants in the female-only FGDs did not mention this, even when probed specifically for this. However, a phone interview with a female adult patient living with her father, was interrupted by the father, who asked that his daughter never be contacted again by the DR-TB program as she was already healed by prayers.

Discussion and recommendations

We conducted qualitative interviews in 4 Nigerian states, combining this with documentary review of guidelines and policies in place within the DR-TB program, in order to explore barriers to access along the pathway to care. Our findings highlight gaps in equity of access to DR-TB healthcare, in terms of approachability, acceptability, availability, affordability and appropriateness. In line with our transformative research approach (Mertens, 2007, Sweetman et al., 2010), this discussion of our findings emphasizes possible interventions to enhance ease and equity of access.

In order to improve case finding and treatment coverage rates, the TB program in Nigeria needs to focus attention at the different contextual and health system factors impeding access. Our study identified several barriers within the current DR-TB health system that impede equitable access along the pathway to care for different groups of patients.

We identified access to information about TB in general, and about the availability of free services in particular, as a major challenge, preventing engagement with the system and leading to prolonged care pathways. A study in Nigeria on health-seeking pathways of TB patients found that the perceived cause of TB influenced their first choice of treatment (Okeibunor et al., 2007). Patients who believed TB was caused by witchcraft were more likely to use alternative treatments. Many participants in our study observed that patients only go the hospital after exhausting other options in the private sector. Treatment delays were, thus, related more to inadequate community education about TB disease and available services, as well as poor health worker attitudes (Okeibunor et al., 2007). Several community health awareness interventions across different disease settings have documented effectiveness, and these include 'edutainment' using media (radio, TV and print), school and community outreaches, dedicated community helplines in local languages, (Sharma et al., 2005, Yassin et al., 2013b, Colvin et al., 2014, Barker and Sabido, 2005, Gopichandran et al., 2010, Piotrow and De Fossard, 2003, WHO, 2015a). These messages need to be tailored to context and culturally sensitive to be effective and will go beyond the current strategies employed by the Nigerian TB program, which include patient educational posters on the walls of facilities and periodic active case finding in communities. The current strategies rely on a TB patient presenting voluntarily at a facility before learning about available services, or through targeted active case finding activities by implementing partners.

Another opportunity for improving equity of access is improving the referral system between the private and public sectors. Nigeria has one of the highest percentage of patients using the private sector as first point of care (66-92%) in the world, with the over 60,000 PMVs in the country (WHO, 2018a). Currently, the TB program has mechanisms in place to meet with representatives from community-based organizations, including traditional and religious organizations, and there are implementing partners working on improving private sector engagement (WHO, 2018a). However, these efforts have not translated to significant improvements in referral between the private and public sector (WHO, 2018a). Current fees-for-referrals from private facilities will need sustained funding, and additional research is needed to find out more about these programs, including coverage and whether information about the scheme is available to all PMVs and private hospitals. As suggested by the respondents themselves, we agree that media engagement is an opportunity to increase public awareness using culturally adapted media programs in different languages to take the information directly into communities where it is most needed.

An immediate step for the National program could include additional address verification for all patients being tested for TB. The TB and DR-TB guidelines currently do not include instructions to public providers on address verification steps, unlike in the South African and Zimbabwean guidelines (TB DOTS Strategy Coordination, 2014, Zimbabwe National TB Control Programme, 2010). Verifying contact information, especially in settings with informal address systems, has potential in reducing loss to follow-up and improving contact tracing (Stalin et al., 2020, Tweya et al., 2010, Weigel et al., 2011). One possibility might for the TB program to ask patients to provide contact verifiable addresses for their treatment supporters on testing to serve as an additional way to contact patients if they become lost to follow-up; this 'guarantors' or 'referees' system has been used successfully by financial institutions in Nigeria and similar settings to recover bad loans (Adeyemo and Osofisan, 2012, Nnamani and Mejeha, Obinna Udodiri et al., 2019, Teshome, 2010). However, operational issues will need to be monitored and addressed to ensure that the benefits outweigh the costs of this additional task in an already overburdened system.

Compared to guidelines from South Africa and Zimbabwe (Zimbabwe National TB Control Programme, 2010, TB DOTS Strategy Coordination, 2014), the guideline from Nigeria would benefit from the inclusion of clearly delineated timelines such as replacing "early diagnosis" with "diagnosis of DR-TB within 48 hours of submitting a sample" and "timely treatment initiation" with "commencement of TB treatment within five days of reporting to a health facility with symptoms of TB". The Nigerian guideline could also benefit from the inclusion of relevant sections from the Nigerian Health Act that give weight to patient's rights or highlight penalties for endangering the health of others by refusing care or preventing them from accessing care. This would protect the rights of women and children identified in our study as having limited autonomy to access care.

As a limitation, we were not able to corroborate that all the documents reviewed were sufficiently available to field staff, and how much these documents influenced their practice, and it might be necessary to evaluate this effect in future research. The major documents with which most of the healthcare workers were familiar were the TB guidelines and workers' manuals. Secondly, the purposive sampling method we used may have introduced selection bias.

Conclusions

Our findings highlight health system barriers around coverage, operations errors, and provider attitudes, with patient financial support as a major facilitator; and patient barriers of awareness, perceptions of poor public sector care, beliefs and preference for alternative care. We discussed several opportunities for improvement to the demand and supply factors impacting access to DR-TB healthcare. Some patient groups appear to be disadvantaged in terms of access to DR-TB care., Using the Levesque framework to examine "ease" (demand) and "equity" (supply) allows for an exploration of subtle dynamics and contextual issues that could potentially be leveraged to improve ease and equity. Given the urgent need to increase notification and treatment coverage, there is a need for the TB program to innovate and reduce these barriers as well as adapting to the needs of the patients, including improving referral system with the private sector, community awareness, and protecting the rights of patients with limited autonomy.

References

ADEYEMO, O. O. & OSOFISAN, A. O. 2012. Empirical Study of Statistical Based Method and Artificial Neural Networks for Credit Rating in Nigerian Banks. *Science,* 3.

ALMGREN, G. 2018. *Health care politics, policy, and services: a social justice analysis*, Springer publishing company.

ANDREWS, J. R., BASU, S., DOWDY, D. W. & MURRAY, M. B. 2015. The epidemiological advantage of preferential targeting of tuberculosis control at the poor. *The International Journal of Tuberculosis and Lung Disease,* 19**,** 375-380.

ARGY, O. 1996. Standards of care. *JAMA,* 275**,** 1296-1296.

BARKER, K. & SABIDO, M. 2005. *Soap Operas for Social Change to Prevent HIV/AIDs: A training guide for journalists and media personnel*, Population Media Center.

BRAVEMAN, P. A. 2003. Monitoring equity in health and healthcare: a conceptual framework. *Journal of health, population and nutrition***,** 181-192.

COLVIN, C., MUGYABUSO, J., MUNUO, G., LYIMO, J., OREN, E., MKOMWA, Z., MAKAME, M., MWANGOMALE, A., MAHAMBA, V. & MUELLER, L. 2014. Evaluation of community-based interventions to improve TB case detection in a rural district of Tanzania. *Global Health: Science and Practice,* 2**,** 219-225.

CRESWELL, J. W., CLARK, V. P. & GARRETT, A. 2003. Advanced mixed methods research. *Handbook of mixed methods in social and behavioural research. Thousand Oaks, CA: Sage***,** 209-240.

EVANS, D. B., HSU, J. & BOERMA, T. 2013. Universal health coverage and universal access. SciELO Public Health.

FMOH 2008. The National Guidelines for TB Infection Control. *In:* HEALTH, D. O. P. (ed.). Abuja, Nigeria.

GIDADO, M., NWOKOYE, N., OGBUDEBE, C., NSA, B., NWADIKE, P., AJIBOYE, P., ENEOGU, R., USENI, S., ELOM, E. & LAWANSON, A. 2019. Assessment of GeneXpert MTB/RIF performance by type and level of health-care facilities in Nigeria. *Nigerian Medical Journal: Journal of the Nigeria Medical Association,* 60**,** 33.

GODDARD, M. & SMITH, P. 2001. Equity of access to health care services:: Theory and evidence from the UK. *Social science & medicine,* 53**,** 1149-1162.

GOPICHANDRAN, V., ROY, P. & SITARAM, A. 2010. Impact of a simple educational intervention on the knowledge and awareness of tuberculosis among high school children in Vellore, India. *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine,* 35**,** 174.

GULLIFORD, M., FIGUEROA-MUNOZ, J., MORGAN, M., HUGHES, D., GIBSON, B., BEECH, R. & HUDSON, M. 2002. What does' access to health care mean? *Journal of health services research & policy,* 7**,** 186-188.

GWATKIN, D. R., BHUIYA, A. & VICTORA, C. G. 2004. Making health systems more equitable. *The Lancet,* 364**,** 1273-1280.

INSTITUTE OF HUMAN VIROLOGY NIGERIA 2017. DR-TB COUGH TO CURE – WHAT WE NEED TO KNOW.

INTERNATIONAL MONETARY FUND. 2019. *Gross domestic product per capita.* [Online]. Available: https://www.imf.org/external/pubs/ft/weo/2019/02/weodata/index.aspx [Accessed 03 May 2020 2020].

KREFTING, L. 1991. Rigor in qualitative research: The assessment of trustworthiness. *American journal of occupational therapy,* 45**,** 214-222.

KRUK, M. E. & FREEDMAN, L. P. 2008. Assessing health system performance in developing countries: a review of the literature. *Health policy,* 85**,** 263-276.

LEVESQUE, J.-F., HARRIS, M. F. & RUSSELL, G. 2013. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *International journal for equity in health,* 12**,** 1.

LEVY, B. S. & SIDEL, V. W. 2013. *Social injustice and public health*, Oxford University Press.

MERTENS, D. M. 2007. Transformative paradigm: Mixed methods and social justice. *Journal of mixed methods research,* 1**,** 212-225.

NBLCP/FMOH. 2015. 2015 Annual Report, National Tuberculosis and Leprosy Control Programme. . Nigeria:.

NBLCP/FMOH. 2019. 2019 Annual TB Report. *In:* PROGRAMME., N. T. A. L. C. (ed.). Nigeria:.

NNAMANI, N. & MEJEHA, R. EFFECT OF LENDING CRITERIA ON FEMALES'ACCESS TO CREDIT FROM BANK OF AGRICULTURE ABIA STATE, NIGERIA.

NTBLCP, F. 2010. Workers' Manual. *In:* FEDERAL MINISTRY OF HEALTH, N. (ed.).

NTBLCP, F. 2017a. Guidelines on the Use of the Shorter Regimen and New Drugs in the Clinical and Programmatic Management of Drug Resistant Tuberculosis and Co-Infections of Nigeria *In:* FEDERAL MINISTRY OF HEALTH, N. (ed.).

NTBLCP, F. 2017b. NTBLCP Xpert machines as at the end of Q3, 2017.

OBINNA UDODIRI, N., JAVED GHULAM, H., HATEM, E.-G., EDWARDS, D. & ERNEST, O. 2019. Dynamics of Group Lending Mechanism and the Role of Group Leaders in Developing Countries: Evidence from Nigeria. *International Journal of Customer Relationship Marketing and Management*.

OGA-OMENKA, C., ZAROWSKY, C., AGBAJE, A., KUYE, J. & MENZIES, D. 2019. Rates and timeliness of treatment initiation among drug-resistant tuberculosis patients in Nigeria-A retrospective cohort study. *PloS one,* 14.

OKEIBUNOR, J. C., ONYENEHO, N. G., CHUKWU, J. N. & POST, E. 2007. Where do tuberculosis patients go for treatment before reporting to DOTS clinics in southern Nigeria? *Tanzania health research bulletin,* 9**,** 94-101.

ORGANIZATION, W. H. 2004. Reaching the poor: challenges for TB programmes in the Western Pacific Region. Manila: WHO Regional Office for the Western Pacific.

PATTON, M. Q. 2007. Sampling, qualitative (purposive). *The Blackwell encyclopedia of sociology*.

PIOTROW, P. T. & DE FOSSARD, E. 2003. Entertainment-education as a public health intervention. *Entertainment-education and social change.* Routledge.

RAINE, R., OR, Z., PRADY, S. & BEVAN, G. 2016. Evaluating health-care equity. *Challenges, solutions and future directions in the evaluation of service innovations in health care and public health.* NIHR Journals Library.

ROSCOE, C., NAMIBIA, C., KALAPILA, A. G., SPACH, D. H. & AETC, M. W. Learning Objective Performance Indicators.

RUBENSTEIN, L., HEMPEL, S., DANZ, M., ROSE, D., STOCKDALE, S., CURTIS, I. & KIRSH, S. 2020. Eight Priorities for Improving Primary Care Access Management in Healthcare Organizations: Results of a Modified Delphi Stakeholder Panel. *Journal of general internal medicine,* 35**,** 523-530.

SEALE, C. 1999. Chap 4: Guiding ideals. *Quality in qualitative research.* Thousand Oaks: Sage Publications.

SHARMA, N., TANEJA, D., PAGARE, D., SAHA, R., VASHIST, R. & INGLE, G. 2005. The impact of an IEC campaign on tuberculosis awareness and health seeking behaviour in Delhi, India. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 1259-1265.

STALIN, P., MANIKANDAN, M., ANTONY, V., MURUGAN, N., SINGH, Z., KISKU, K. H., PURTY, A. J., VASUDEVAN, K., CHERIAN, J. & BABU, V. 2020. Identifying and addressing factors contributing to pretreatment loss to follow-up of tuberculosis patients referred for treatment from medical colleges in Pondicherry: An implementation research. *Indian Journal of Community Medicine,* 45**,** 27.

SUBBARAMAN, R., NATHAVITHARANA, R. R., MAYER, K. H., SATYANARAYANA, S., CHADHA, V. K., ARINAMINPATHY, N. & PAI, M. 2019. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLoS medicine,* 16.

SWEETMAN, D., BADIEE, M. & CRESWELL, J. W. 2010. Use of the transformative framework in mixed methods studies. *Qualitative inquiry,* 16**,** 441-454.

TB DOTS STRATEGY COORDINATION 2014. National Tuberculosis Management Guidelines. *In:* HEALTH, N. D. O. (ed.). Republic of South Africa: Dept of Health, RSA.

TESHOME, D. 2010. *Non-performing Loan and Its Management in Ethiopia: A case study on Dashen Bank Mekelle Area Bank, in Tigray.* Mekelle University.

THE WORLD BANK. 2016. *Current health expenditure (% of GDP) - Sub-Saharan Africa* [Online]. Available: https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?contextual=max&locations=ZG-1W [Accessed 05 May 2020 2020].

TONG, A., SAINSBURY, P. & CRAIG, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International journal for quality in health care,* 19**,** 349-357.

TWEYA, H., GARETA, D., CHAGWERA, F., BEN-SMITH, A., MWENYEMASI, J., CHIPUTULA, F., BOXSHALL, M., WEIGEL, R., JAHN, A. & HOSSEINIPOUR, M. 2010. Early active follow-up of patients on antiretroviral therapy (ART) who are lost to follow-up: the 'Back-to-Care'project in Lilongwe, Malawi. *Tropical Medicine & International Health,* 15**,** 82-89.

WEIGEL, R., HOCHGESANG, M., BRINKHOF, M. W., HOSSEINIPOUR, M. C., BOXSHALL, M., MHANGO, E., NKWAZI, B., TWEYA, H., KAMLAKA, M. & CHAGWERA, F. 2011. Outcomes and associated risk factors of patients traced after being lost to follow-up from antiretroviral treatment in Lilongwe, Malawi. *BMC infectious diseases,* 11**,** 31.

WHO 2010. *Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies*, World Health Organization.

WORLD HEALTH ORGANIZATION 2010. *Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies*, World Health Organization.

WORLD HEALTH ORGANIZATION 2015. Digital health for the End TB Strategy: an agenda for action. World Health Organization.
WORLD HEALTH ORGANIZATION 2018. Engaging private health care providers in TB care and prevention: A landscape analysis. *Geneva: World Health Organization*.
WORLD HEALTH ORGANIZATION 2019. Global tuberculosis report 2019.
YANG, W.-T., GOUNDER, C. R., AKANDE, T., DE NEVE, J.-W., MCINTIRE, K. N., CHANDRASEKHAR, A., DE LIMA PEREIRA, A., GUMMADI, N., SAMANTA, S. & GUPTA, A. 2014. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberculosis research and treatment,* 2014.
YASSIN, M. A., DATIKO, D. G., TULLOCH, O., MARKOS, P., ASCHALEW, M., SHARGIE, E. B., DANGISSO, M. H., KOMATSU, R., SAHU, S. & BLOK, L. 2013. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. *PloS one,* 8.
ZIMBABWE NATIONAL TB CONTROL PROGRAMME 2010. National Tuberculosis Guidelines. *In:* HEALTH, N. D. O. (ed.). Republic of South Africa: Zimbabwe National TB Control Programme,.

CHAPTER 6: DISCUSSION

6.1 Overview of results

Nigeria, a high burden HIV, TB and DR-TB country, has disturbingly low rates of TB notification and treatment, despite providing free DR-TB care since 2011. This threatens global and national TB control strategies, making case detection a priority for the Nigerian TB Control program. I decided to focus on DR-TB for three main reasons. DR-TB diagnosis and treatment coverage in Nigeria is much lower than for drug susceptible TB. Whereas 25% of incident TB cases were detected in 2018, only 11% of incident DR-TB were detected in the same year. Of these, nearly all TB notifications, and only 81% of DR-TB diagnosed patients were placed on treatment in 2018 (WHO, 2019a). Our study revealed that on average, between 2013 to 2017, only 64% of diagnosed DR-TB patients were ever placed on treatment. There is also evidence that DR-TB care is more difficult to implement by health systems and its treatment more toxic and challenging to patients. Lastly, my experience with DR-TB program implementation in Nigeria gave me a unique insight into the challenges of implementation.

As mentioned in the introduction, the purpose of this dissertation was to understand reasons for low case detection and treatment rates for DR-TB in Nigeria by questioning the health system and patient factors that influence diagnosis and treatment for DR-TB in Nigeria; the percentage dropouts at each stage of the DR-TB care cascade and reasons for this; and whether the policies, structures and procedures for DR-TB care are equitable for different patient socio-demographic groups.

To achieve these objectives, I started with a review of current literature on barriers to DR-TB treatment in sub-Saharan Africa, using complementary methodologies of systematic review and qualitative meta-synthesis. Then, I designed and conducted a mixed methods transformative empirical study. I conducted a cohort analysis of timely treatment for patients diagnosed with DR-TB in 2015; using quantitative and qualitative data, I estimated the DR-TB care cascade and explored the individual and health system factors associated with being retained in care; and examined whether existing health system policies, structures and processes were equitable for different sociodemographic groups. The analyses were conducted using secondary data and documents from the National TB program, as well as qualitative interviews with patients, treatment supporters, providers and program managers in 4 Nigerian states.

This chapter discusses the key findings in the larger context of the study objectives and the field of DR-TB as a global public health challenge. I also recapitulate the key messages of each article and how the findings are integrated. Additionally, I present some implications for research, policy and practice. Finally, I discuss the study strengths and limitations.

6.1.1 Literature review

In the literature reviews, presented in Articles 1 and 2, several patient, community and health system factors were identified as causes of low TB diagnosis and treatment. Health system factors like laboratory infrastructure, sputum transportation, health product supply chain, personnel technical knowledge and turn-around time were major recurring themes across all study types. However, patient factors like poor knowledge of the disease, attitudes and beliefs including fear of stigma, perception of inadequate quality of care, and gender norms were barriers to case finding. Several facilitators were identified to improve case finding including decentralization of services and integration with other health services, community awareness and screening campaigns.

Several differences between TB and DR-TB care emerge in the literature. DR-TB literature reflected more difficulties with accessing diagnostic services, the large number of health system processes necessary to initiate care, hospitalization that is sometimes required, and more side effects than is the case for drug susceptible TB. Facilitators particularly relevant to DR-TB care included the availability of newer diagnostics like the GeneXpert, and a substantial patient financial support system in some countries, including Nigeria.

However, both reviews reveal a paucity of data on access barriers to TB services in Nigeria, particularly as the country has the highest burden of TB and DR-TB in Africa, and the lowest case detection rate in the region (WHO, 2019a). Qualitative data exploring factors influencing access to TB care is scant from Africa in general, and Nigeria in particular. More qualitative data would provide the needed insight into the contextual barriers behind the missing TB cases, particularly for DR-TB, whose diagnosis and treatment are more specialized. This might be due in part to a historically higher global health focus on newer diagnostics and treatment innovations, than on implementation science and the social determinants of health (Ortblad et al., 2015, Wingfield et al., 2016). Although the 2015 WHO's End TB Strategy highlighted the need to address the social determinants of TB, (Uplekar et al., 2015), TB research in Nigeria is still lagging.

6.1.2 Predictors of timely treatment

The World Health Organization (WHO) recommends treatment initiation within 4 weeks of diagnosis, as DR-TB treatment outcomes are optimized by timely diagnosis and treatment (WHO, 2016b). In Article 3, we estimated the proportion and characteristics of patients not initiated on treatment within one month of diagnosis in 2015, in response to research objective 1, to compare the socio-demographic characteristics of the patients diagnosed in 2015 who were treated with those untreated. We performed logistic regression of using diagnosis (GxAlert) and treatment (e-TB Manager) data at the national level, with a subsequent sub-analysis of the South West zone, as this zone had the highest proportion of notified DR-TB patients compared to other zones. Predictors of any treatment initiation included patients' geographical location (South West geopolitical zone and Ogun State), and children were more likely than adults in the South West zone. Predictors of timely treatment were semi-urban geographical location, in-patients (compared to those initiated in the community), and new patients (compared to retreatment, default or relapsed patients).

Quantitative findings (cohort and cascade analysis) suggest that that the TB providers, especially in the northern parts of Nigeria, and the State teams responsible for community enrolment, need to be especially targeted with training to improve treatment enrolment.

6.1.3 Cascade of care

Article 4 describes the DR-TB care cascade in Nigeria, addressing objectives 2 and 3. On average, between 2013 and 2017, about 80% of estimated DR-TB incident cases never access testing, due mainly to inadequate awareness about the disease and location of DR-TB care services, as well as inadequate coverage of services. And, although patients were using the private sector, including private hospitals, patent medicine stores and traditional healers, there was very low linkage to care from this sector. Patients were spending large amounts on care and months to years before finding the right care, if ever. Of those tested, 75% of were not diagnosed. This was due to provider attitudes, clinic and laboratory challenges, and data errors. Patients also mentioned fear of prolonged treatment. Most of those diagnosed (64%) went on initiate treatment and 78% of these finished treatments. Within the cascade, treatment completion once diagnosed was higher in adults, males and patients in the south west geopolitical zone.

Although DR-TB incidence was higher in adult males, women and children faced particular challenges in accessing care due to a lack of autonomy and adverse gender norms. Patients living in rural areas experienced transportation challenges in accessing care.

These results suggest the need for aggressive community mobilization and education on TB and availability of services, private sector engagement and training of providers.

6.1.4 Ease and Equity of Access

Finally, I also examined the ease and equity of access to DR-TB care, in response to objective 4, which aimed to describe health systems policies, structures and procedures for DR-TB care and how these relate to diagnosis and treatment for different patient socio-demographic groups. The results are presented in Article 5. Our findings showed barriers in access to DR-TB healthcare in terms of approachability, acceptability, availability, affordability and appropriateness. Several sociodemographic groups, including children, women, workers, those in rural communities far from TB healthcare, and students faced more impediments to care. These were mainly due to poor linkages with the private sector, patient distrust of public healthcare, workplace rigidity, unavailable clinic hours for patients who go to school during the day and negative cultural norms.

We suggest revising the current workers guidelines and interventions that target improving community awareness and engaging the private sector.

6.2 Integration of findings

Overall, the studies in this dissertation provide significant empirical evidence that highlights areas for interventions to improve the access to DR-TB healthcare in Nigeria. The findings allow us to better understand patient, community and health system barriers to care. While every level of care is important, our analysis reveals that efforts need to be concentrated in getting patients tested and diagnosed.

The transformative mixed methods design of this study aimed at using each type of data and analysis to inform others, all within the patient-centered ease and equity of access theoretical lens. Data from the systematic review and qualitative meta-synthesis informed the initial study design, variables and instruments, as well as the conceptual framework; the cohort analysis highlighted the need for a cascade analysis and influenced qualitative interview questions and sampling strategy. The cascade analysis highlighted the gaps between each stage of the care continuum, while the qualitative findings explored the health system and patient level determinants of access to care. Using different sources of data and analysis highlights the utility of mixed methods in producing richer and more useful results, by applying different lenses at a problem, which in our case is access to DR-TB healthcare in Nigeria. The contribution of each article to the research goals is shown in *figure 21*.

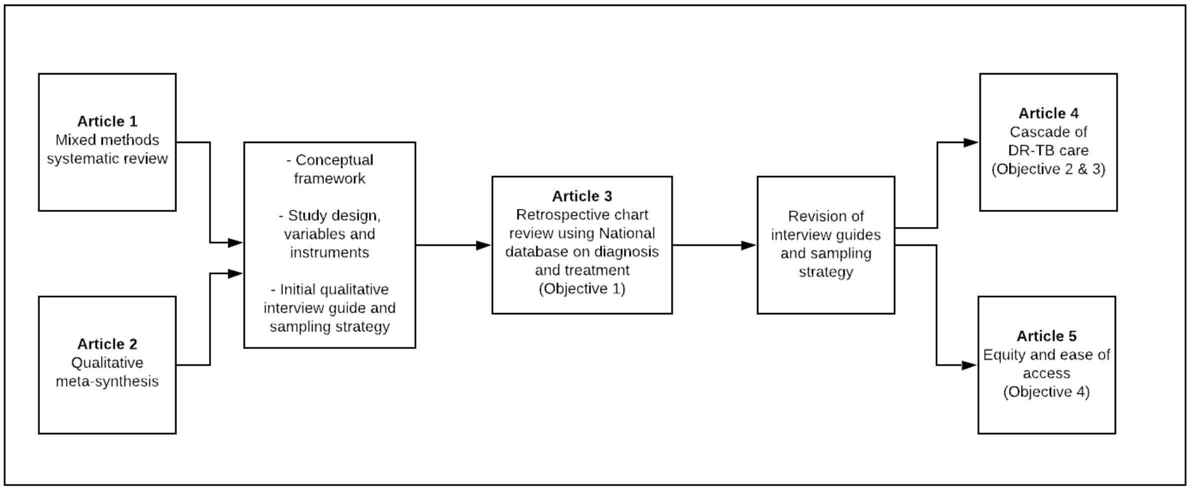


Figure 21. – The contribution of each article to the research objectives

The conceptual framework, discussed in Chapter 2, was very useful in keeping the theoretical lens at the centre of data collection and analyses. It allowed an in-depth exploration of the different factors that contribute to poor access at the health system and patient levels. Unpacking the various building blocks within the health system, and the patient characteristics that influence health behaviour was useful in separating barriers and would be helpful for targeted interventions.

The main findings from the different aspects of the research are illustrated in Figure 22.

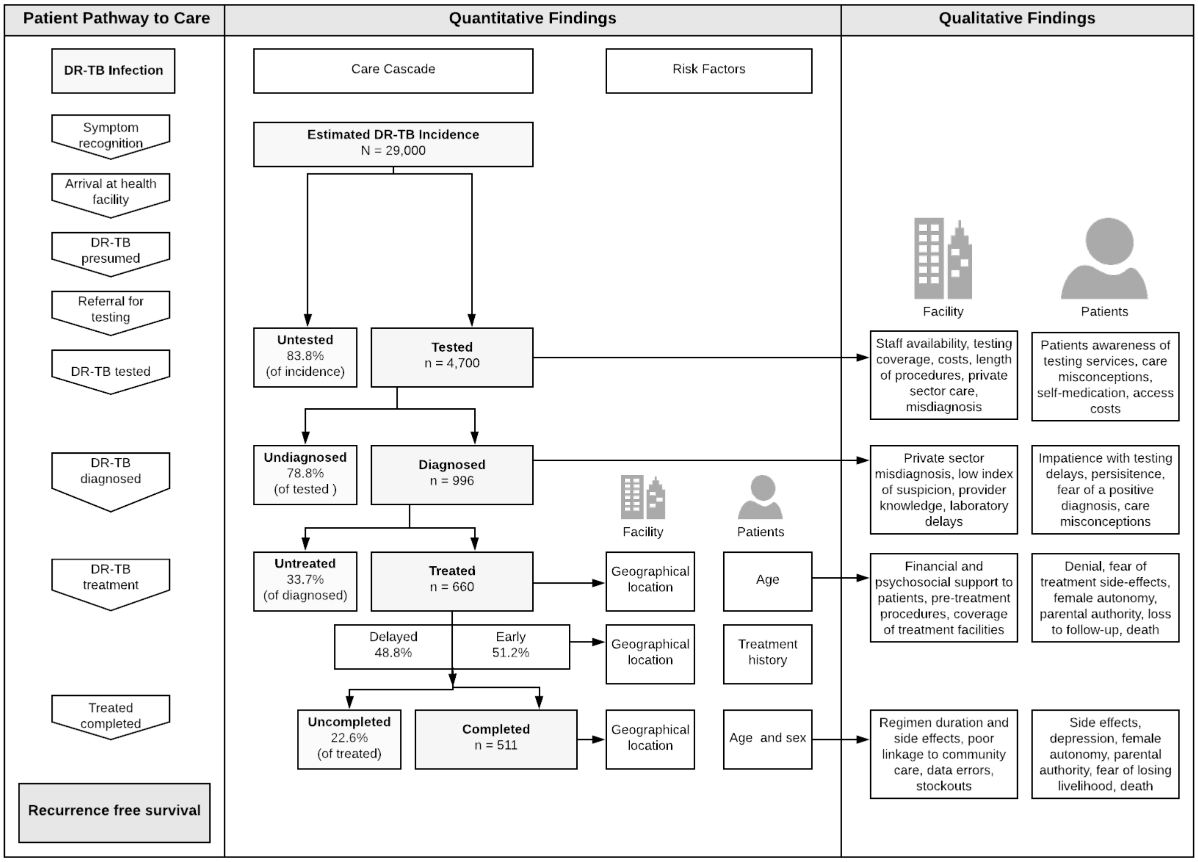


Figure 22. – Determinants of DR-TB from quantitative and qualitative phases

Findings from the quantitative phase suggest that geographical location of the facility, and patients' treatment history, age and sex can act as barriers to care. Patients in the Southwest zone were more likely than those in other zones to access care. Possible explanations from interview data include program maturity, team motivation and organization around DR-TB case notification. For children, for whom limited access was observed in the cascade analysis, parents' distrust of public healthcare was a recurring theme from providers and patients.

The qualitative interviews highlighted quantitative findings related to patients' age and sex, as well as some regional differences in practices and care team dynamics. However, we were unable to explore further the quantitative finding indicating that new patients were more likely to initiate treatment than those with unknown TB treatment history or those who defaulted from first line treatment. One possible reason could be that patients who default from treatment are likely to have more challenges accessing care than other patients, manifesting in the delay they experience in initiating DR-TB treatment.

The cohort analysis showed that in the Southwest zone, children were more likely than adults to get treated once diagnosed. Program managers mentioned that during scaleup of treatment, pediatric care technical assistance was provided to healthcare workers, with emphasis on the Southwest zone, which had the highest number of patients. This could be partially responsible for the improved care at this stage of care (treatment initiation) and in this region. Although healthcare workers mentioned that women were likely to have more barriers due to a lack of autonomy, the female patients interviewed did not mention this as a barrier. This could be due to their perceptions about culture and rights, or it might be that this was community-specific, and not in the communities we sampled.

The cohort analysis highlights the broad strokes of treatment initiation and the importance of history (geopolitical zones – and their histories of program implementation, resourcing, and conflict – as well as the patient history). The cascade of care quantitative analysis reveals the influence of age and gender on access, which might not always be obvious without looking at the whole process of care. The cascade gap analysis allows patients and programmes to look at what happens in and between steps in care for a complex disease needing lengthy care.

The ease and equity of access paper, Article 5, returns to our adapted Levesque conceptual framework to demonstrate the utility of the paired access dimensions in helping to explain how systems, patients and contexts interact, in tandem. This allows us to go beyond a supply "versus" demand dichotomy, and it also allows us to see the relative importance of different elements without falling into the trap of focusing on one looming issue.

There were several other barriers mentioned in the qualitative phase that were not analysed in the quantitative phase, including spiritual beliefs, preference for alternative care, including self-medication, as well as work and school conflicts. The secondary data used for the quantitative analysis were not disaggregated by religion or occupation to allow for these analyses.

6.3 The relevance of our conceptual framework

We adapted our conceptual framework (*figure 23*) from several studies on access, TB care continuum and cascade as well as the characteristics and interactions between health systems and patients. We applied these frameworks to our overall study objectives, which was to understand barriers and facilitators to DR-TB care.

Several conceptualizations of access exist in literature, focusing on various dimensions of access including financial, physical and geographical accessibility, personal, time and organizational factors, quality of care, coverage, utilisation, acceptability, adequacy, affordability and availability (Dutton, 1986, Penchansky and Thomas, 1981, Shengelia et al., 2003, Aday and Andersen, 1974). Our framework uses the Levesque conceptualization at its foundation, as it builds on many of these previous work (Levesque et al., 2013). As discussed in Chapter 2, the Levesque framework pairs the interactions between the patient abilities and health system accessibility.

We also considered two additional approaches- the intersectionality framework (Hankivsky, 2012, Gilson, 2012, Simpson, 2009) and the Andersen, Aday and Newman Behavioural models (Andersen and Newman, 2005, Aday and Andersen, 1974). The Andersen model allowed us to probe the individual level factors and behaviours more deeply than the Levesque framework does.

We initially assumed that an intersectionality analysis would best explain how demographic characteristics such as gender, poverty, race or ethnicity were interacting in complex ways, to increase vulnerability and disadvantage for different patient groups, and offer direct policy-relevant analyses and recommendations. However, in our particular context, several components needed for an intersectionality analysis - discriminations that impact identity, power dynamics, and structures that reinforce exclusion - were missing from our data.

- Discriminations that impact Identity – While there were cultural norms discriminating against women and minors, there were no obvious health system discriminations based on identity.

- Power dynamics – The existing health system discriminations were due to disease status and not identity, making it difficult to undertake a power analysis. A power analysis would have been more feasible if our study included how community factors were affecting access to care.
- Structures that reinforce exclusion - Based on interviews with patients, relatives and health care workers, the DR-TB system did not directly exclude any particular patient groups

As discussed in Chapter 2, we used the WHO health system building blocks framework to further explore the health system factors, as this allowed us to break down the different components within the health systems that are relevant to patients access - service delivery, workforce, information management system, health products, financing, leadership and governance (WHO, 2007, WHO, 2010b).

It was necessary to examine how these patient and health system factors interplayed with the patients' pathway to care. To do this, we used the concept of the continuum of care – from symptom onset to treatment completion- and the cascade of care including incidence, testing, diagnosis, treatment and recurrence free survival (Roscoe et al., 2020, Yang et al., 2014).

Taken together, these concepts highlighted the interplay between health system and patient factors into paired dimensions that have implications at each stage of the care cascade (*figure 23*). We also examined the equitability of health systems and the ease of access from the individual point of view.

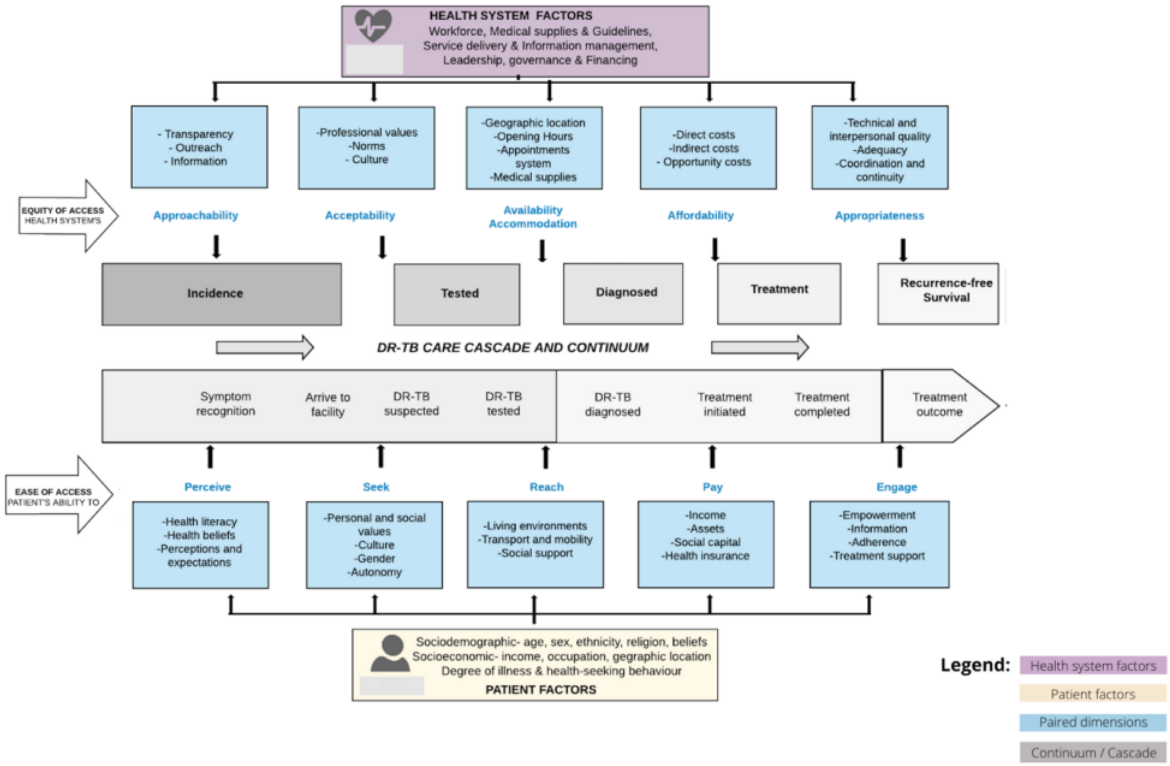


Figure 23. – Our conceptual framework is divided into 4 main concepts

The conceptual framework was relevant to each of our study objectives in different ways, as shown in *Figure 24*.

The first objective was aimed at understanding the predictors of access, using the sociodemographic differences between patients who were treated versus those who were not among those diagnosed using available variables in our secondary data. Our analysis related to this research objective relied on the concepts of the care cascade, as well as patient and health system factors. As discussed in *Article 3*, our findings were limited to the available variables in our secondary data.

The second and the third objectives aimed to quantify gaps at each step of the care cascade and identify reasons for these gaps from the perspectives of patients, their relative and healthcare workers. For these objectives, every aspect of our conceptual framework was relevant - the patient and health system factors, and the care cascade. The results and discussions in *Article 4* highlight the usefulness of our framework.

The fourth objective was to describe the equitability and ease of DR-TB care access based on the prevailing health system policies, structures and procedures. Equity, focusing on the health system to ensure equal services for patients in equal need, and ease, focusing on individual and societal barriers to available healthcare services, aligned directly with the Levesque paired dimensions of access.

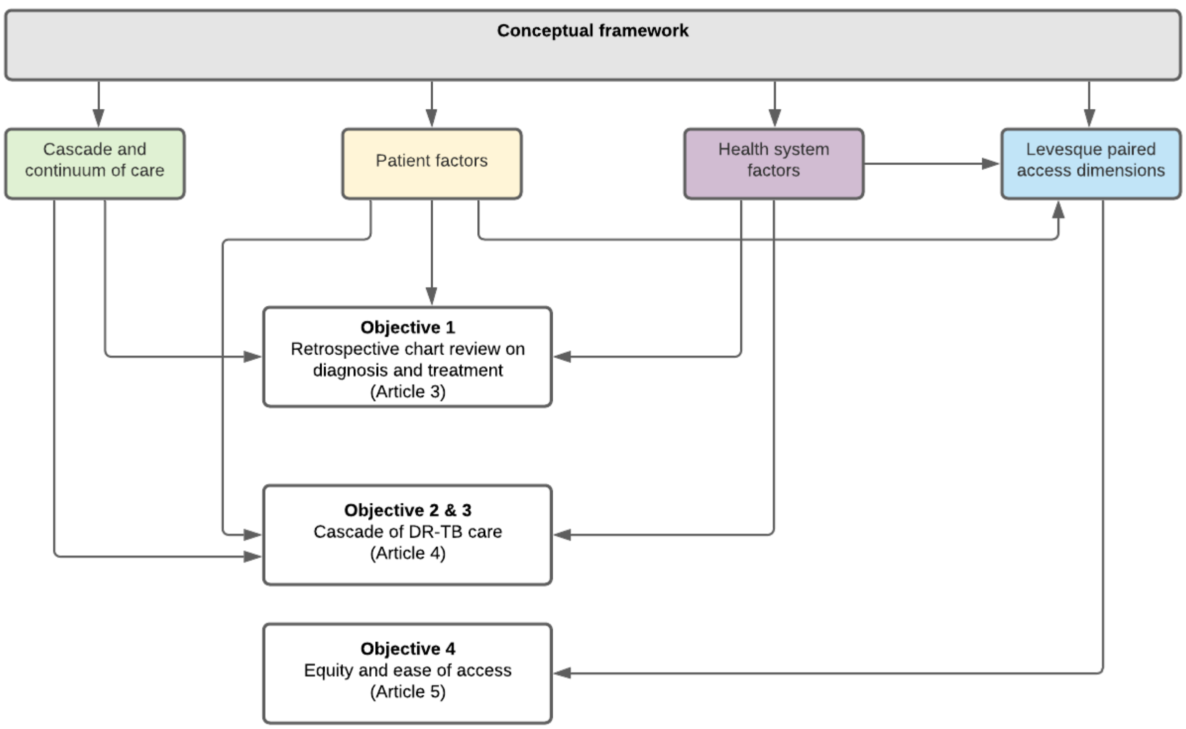


Figure 24. – Aligning the four concepts to our research objectives

6.4 Implications for research

This dissertation adds to the growing but still limited body of evidence on the barriers and facilitators to DR-TB care access.

Whilst initially this study sought to examine access to timely treatment initiation for people diagnosed with DR-TB, low testing and access to diagnosis emerged as the major barriers to care. These highlight poor awareness, distrust of healthcare services, and beliefs on the patient level. Some reasons for low access to testing at the health system level were the suboptimal linkages between the public and the private sector, laboratory and clinic operational challenges, inadequate provider knowledge, skills and attitudes in Nigeria. Treatment coverage and completion were also suboptimal. These were due to coverage of treatment services, pre-treatment procedures, inadequate psychosocial support to the patients, treatment duration and side effects, poor linkage from the hospital phase to the community phase of treatment. They were also due to patients' experience of side effects, negative female autonomy and parental influences, loss to follow-up and or death.

Research on access to diagnosis needs to sample broadly and have specific questions for the service in question. In order to study people who did not have access to diagnosis, the study has to sample people, who for whatever reason, could not access testing. TB-specific population surveys or community interviews may be better suited to investigate for this type of inquiry. The Demographic and Health Surveys (DHS) Program for Nigeria could provide a powerful sampling frame for such work. However, the DHS for Nigeria has historically had very limited information on TB, from 1990- 2018, focusing only on childhood vaccination for TB (USAID DHS Program, 1990, USAID DHS Program, 1999, USAID DHS Program, 2013, USAID DHS Program, 2018). It does not have the focus on the access barriers necessary to understand barriers to TB diagnosis. Also, while our study had two community interviews, we believe that a larger number of this type of qualitative interviewing will yield more nuanced results.

Access to TB diagnosis and treatment in sub-Saharan Africa and other settings has been associated with many of these factors, and even where treatment is provided free, as in our study (Finnie et al., 2011, Kemp et al., 2007, Cazabon et al., 2017a, Chimbindi et al., 2015, Mauch et al., 2013, Onazi et al., 2015, Ukwaja et al., 2013b).

Drug resistance adds several layers of difficulty in managing TB. DR-TB has been shown to share many of the same barriers to care that drug-susceptible TB has – catastrophic indirect costs of care, distance to facility, use of alternative care and negative gender norms on the patient side (Chimbindi et al., 2015, Kemp et al., 2007, Mauch et al., 2013, Onazi et al., 2015, Ukwaja et al., 2013b, Cambanis et al., 2007, Ukwaja et al., 2013c, Finnie et al., 2011, Munro et al., 2007, Chileshe and Bond, 2010); and stigma, inadequate provider knowledge and numbers, poor coordination, referrals, and service integration, as well as logistical shortages on the health system side (Okot-Chono et al., 2009, Sullivan et al., 2017). However, DR-TB patients incur up to nineteen-fold higher indirect costs (clinic visits, drugs, transports, income loss and other - hospitalization, food, accommodation, traditional medicine, vitamins etc.) (Laurence et al., 2015, Tanimura et al., 2014), and this was higher during the intensive phase of treatment and for in-patients compared to the continuation phase and out-patient (Ramma et al., 2015). In a systematic review, one study found that 23% of DR-TB patients defaulted due to financial constraints, while another found 50% of patients unemployed even after a year of treatment; with caregivers often giving up work to care for their loved ones (Thomas et al., 2016). The long treatment duration, complexity and medication side effects that treatment for DR-TB entails, as well as the inadequate coverage of specialized clinic requirements for diagnosis and treatment, were responsible for the socioeconomic and psychological toll borne by patients including the increased travel times and transport costs, depression, and psychological distress (Thomas et al., 2016).

Health system barriers were also more pronounced due to the increased technological needs for diagnosing DR-TB and professional care for patients on treatment – pre-treatment assessments (audiometry, liver function, chest radiograph, full blood count, drug sensitivity etc.), need for daily injectables during the intensive phase, side effects management etc.) (WHO, 2014a). The current programmatic direction led by the WHO for shorter regimens will reduce some of the noted health system barriers (WHO, 2019e).

Facilitators to care from other resource-limited settings, and in Nigeria were similar to those found in our study (Oshi, 2009, van Hoorn et al., 2016) - socioeconomic support to patients to improve treatment outcomes (van Hoorn et al., 2016); free decentralized care (Ebonwu et al., 2013); and increasing provider and patient knowledge of DR-TB disease and services (Mpagama et al., 2013, Naidoo et al., 2015a). More qualitative research might be necessary to identify additional facilitators to care and the role of treatment support especially amongst patients who complete treatment.

More studies may confirm or provide additional insight into how certain types of occupations are more at risk of poor access, and on how contextual factors, including community beliefs, especially in Northern Nigeria, might be impeding access, as indicated in the quantitative analyses.

It might also be relevant to do additional quantitative research in our setting on other predictors of access noted in literature, including income, household occupation, and level of education. Our secondary data did not include these socioeconomic variables to allow for a more detailed analysis.

Socioeconomic status measurements for research purposes can often be challenging (Pritchett, 2006). While the World Bank has set the standard for international poverty as living on $1.90 a day (The World Bank, 2015), many households, especially in the developing world, do not have adequate consumption or expenditure data to determine personal and household income (Filmer and Pritchett, 2001). Some authors have proposed certain wealth proxies as a “control” variable in estimating household wealth, such as nutritional status, employment, maternal or personal educational level, number of household assets, number of children in school, type of housing (Hassan and Babu, 1991, Filmer and Pritchett, 2001). In some developing countries, rural living versus urban can be considered a predictor for poverty. For example, several African countries showed stark differences between rural and urban dwellers in terms of poverty and living standards (Sahn and Stifel, 2003, Anyanwu, 2005). While our study explored the differences between rural to urban populations in terms of DR-TB access, we were not able to adequately relate this to socioeconomic status.

We also recommend that different interventions targeting identified access barriers be tested in different communities in Nigeria. Interventions targeting behavioural change for health, including participatory community and school awareness campaigns are particularly needed. We anticipate that additional information from these research activities will enable the National TB program to target limited resources appropriately and efficiently.

6.5 Implications for policy and practice

There are several policy and practice implications from this dissertation. The key findings show dramatic gaps in the care cascade due to several factors in the DR-TB care system, and some limitations from the patients themselves.

Firstly, looking at the DR-TB care guidelines, our findings show that there is no mention of actions to take when the health of the public or disadvantaged groups are at risk due to the actions of guardians or the patients themselves. For example, if a patient refuses treatment for himself or for his spouse or child, there is not enough in the guideline currently to help practitioners address these types of decisions which adversely affect patient and public health outcomes. We recommend a guideline review for TB care in Nigeria, to highlight the rights of patients, and necessary procedures to manage patients who refuse treatment, or whose autonomy to access treatment are at risk.

Secondly, these findings reveal that even where patients do not know about particular DR-TB services, they do interact with a care system, particularly in the private sector- patent medicine vendors, community pharmacies, private hospitals, traditional healers and faith-based organizations. The private sector needs to be prioritized as stakeholders by the National Program and practical, context-specific engagement targeted at various aspects of this sector. Some actors and institutions of the private sector are not specifically for health (e.g. prayer houses), are currently poorly regulated (e.g. traditional healers) or are not necessarily trained health workers (patent medicine vendors) (Beyeler et al., 2015, Iyalomhe and Iyalomhe, 2012, Oyebola, 1980, Oluwabamide and Umoh, 2011). Some ways to engage with the private sector have been proposed by the WHO and include fees for every referral (WHO, 2018a).

Patient tracking using address verification might be another area that could have cross-cutting impact on the cascade of care, reduce loss to follow-up and improving contact tracing (Stalin et al., 2020, Tweya et al., 2010, Weigel et al., 2011). Asking patients for both their contact addresses and that for their treatment supporter, both of which the health system can verify, could serve as an additional way to contact patients if they become lost to follow-up (Adeyemo and Osofisan, 2012, Nnamani and Mejeha, Obinna Udodiri et al., 2019, Teshome, 2010). However, this could have operational issues that will need to be monitored.

In some settings, including in other disease areas such as HIV, community awareness and cultural barriers have been overcome with context-specific educational entertainment, school and community outreaches, and dedicated community helplines in local languages (Sharma et al., 2005, Yassin et al., 2013b, Colvin et al., 2014, Barker and Sabido, 2005, Gopichandran et al., 2010, Piotrow and De Fossard, 2003, WHO, 2015a). The patients in this study also suggested their own role as potential community advocates. It might also be useful to systematise the involvement of community leaders in DR-TB care. The TB control program could engage community leaders, where necessary, to intervene in families with patient-level barriers like denial, lack of patient autonomy to make health decisions, and default.

Laboratory delays were due to delay in sputum deterioration, contamination, transportation and processing, as well as communication of results back to the requesting TB centre. There were challenges that limited the effectiveness of the GxAlert system in reducing delays in results communication, including internet connectivity issues, non-adherence to algorithms, low utilization rates especially in public facilities and high error rates especially in private facilities (Gidado et al., 2019, Gidado et al., 2018). Continued monitoring and supervision, equipment maintenance, as well as training and retraining of laboratory staff on communication and health logistics is needed to optimize the potential of the system (Gidado et al., 2019, Gidado et al., 2018).

6.6 Strengths and limitations

One of the main strengths of this study is the use of mixed methodology. This, in combination with the researcher's long-term experience in the study context balanced by several years of distance from the field, and enhanced its rigour and validity. By triangulating quantitative and qualitative data sources, we were able to explore different and complementary information on the problem of DR-TB care access in Nigeria. In the quantitative phase, we analysed data from all patients diagnosed with DR-TB in 2015. Findings from this phase was used to revise interview questions for the qualitative phase. We also tracked and interviewed 'negative cases' (diagnosed but untreated patients) from the 2015 cohort.

Another strength of this thesis is the use of a case study methodology for the qualitative phase. This allowed the use multiple sources of data, with maximum variation within each type of data source. We collected data from patients, community members, patient relatives and different healthcare workers. We also analysed data from different documents – treatment guidelines, workers manual, program data on case notification and coverage of services. This allowed for a well-rounded snapshot of the program.

I also adapted and used the same conceptual framework, which was drawn from an extensive review of literature, to analyze and guide both phases of the empirical studies. These findings shed further light on the existing literature and on contextual issues influencing DR-TB care in Nigeria. In particular, using the Levesque paired characteristics on one hand, and the cascade and the WHO building blocks on the other, allowed a deeper understanding of how the supply and demand sides interacted with patient pathways.

While several studies have been done to explore barriers and facilitators to TB care in Africa, to my knowledge, this is the first study focusing specifically on Nigeria's DR-TB care, and cascade analysis. Our mixed methods systematic review was also the first published systematic review on DR-TB care in sub-Saharan Africa.

The overall mixed methods study had several limitations noted below.

The study was not designed to explore access to testing. It was designed primarily to understand barriers and facilitators to treatment following diagnosis. As most of our qualitative data highlighted testing and diagnosis as the major barriers to DR-TB care in Nigeria, further research may be needed to fully explore these access factors.

The quantitative analysis relied on secondary data, and this limited the number of variables assessed to only those collected in the data. There were other variables of interest, identified in literature as determinants of healthcare access in Nigeria that could not be assessed. These include patients' income, and educational level. Other measures like religion and ethnicity might have improved the understanding of potential contextual factors in play.

Our study is also limited by the inclusion of patients and healthcare providers from only the South West and the North Central geopolitical zones. As Nigeria has many cultural differences between regions, interviewing informants from especially the North West or North East zones would likely have provided more insight into the cultural barriers to care in those regions. Although this was likely mitigated by interviewing program managers and implementing partners with National oversight, it is possible that community perspectives from these regions would have given us a more complete picture. Including these additional participants would have required additional funding, not available to the research team at the time.

6.7 Conclusion

The overall aim of this dissertation was to shed more light on the persistent challenges with treatment initiation for free DR-TB care in Nigeria, looking at the care cascade and highlighting gaps in care related to both patients and health systems, and using an equity-focused transformative approach. It lays a foundation for other research, and for action, targeted at improving diagnosis and treatment for DR-TB. Improving case finding and treatment for DR-TB is critical if Nigeria is to consolidate gains in diagnostic technologies and newer treatments.

The fact that the provision of free DR-TB treatment starting in 2011 has not maximised the potential for increased diagnostic and treatment coverage, suggests the need to understand the how patients and their communities interact with the TB healthcare system. Additionally, DR-TB continues to lag behind DS-TB in terms of diagnostic and treatment coverage. This study is significant, as it addresses this critical gap in accessing care in Nigeria. It provides insight needed by policymakers and implementing partners to address systemic disparities and provide more equitable services based on need of the population. The findings will help address the 80% gaps in testing and diagnosis, and the 30% gap in treatment.

The study findings have significant implications for private sector engagement, community awareness strategies, strengthening clinic and laboratory operations, as well as protecting the rights of vulnerable patients.

This study also highlights the strength of using mixed methods to explore multiple dimensions of healthcare access and equity. The transformative design was aimed at promoting social justice and protecting the rights of vulnerable populations in Nigeria.

Finally, this study focusing on Nigeria and justice for its vulnerable populations contributes to the field of global health more broadly. As Nigeria is a major contributor to the global burden of TB and DR-TB, Nigeria's gains – and losses – are also gains or losses for global health, and lessons learned from and with Nigeria can inform research, policy and practice beyond Nigeria's borders.

POSTSCRIPT: GLOBALISATION, COVID-19 AND TB CARE

The role of transnational influences on health is well documented in literature, and is in fact one of the cornerstones of global health practice (Koplan et al., 2009). Transnational mobility can result in dynamic intersections with inequality, and health (Koehn, 2018, Sargent and Larchanché, 2011). This is highlighted by the COVID-19 pandemic which is projected to result in increased cases and 10%, 20%, and 36% more deaths from HIV, TB and malaria, respectively, in 5 years compared to the pre-COVID-19 era (Hogan et al., 2020). For TB, this could mean additional 6 million new cases and 1.3 million deaths in 5 years (StopTB, Pai, 2020a). In high burden settings, low resource settings like Nigeria, this has alarming implications for TB control.

The commentary below, which has been accepted for publication in the *Healthcare Journal*, itemises some of the ways the COVID-19 pandemic threatens TB control, and presents some opportunities for healthcare systems to mitigate these challenges.

The implications for the COVID-19 disruptions in TB care are still emerging. One thing that appears to be clear, though, is the need for longer-lasting strategies in integrating care for the two infections, which have some similar infection patterns and diagnostic technology, beyond emergency care.

Commentary: Lessons from the COVID-19 global health response to inform TB care

Title page

Corresponding author's name: Charity Oga-Omenka

Each author's affiliation and qualifications:

Charity Oga-Omenka[1,2,3] B.Pharm, MPH, Azhee Tseja Akinrin[4] B.Pharm, MPH, Jody Boffa[2,4] PhD, Petra Heitkamp[2,5,] MSc, Madhukar Pai[2,6] MD, PhD, Christina Zarowsky[1,7,8] MD, PhD

1. École de santé publique de l'Université de Montréal (ESPUM), Canada
2. McGill International TB Center, Montreal, Canada
3. Centre de recherche en santé publique, Université de Montréal (CReSP), Canada
4. Azhee Akinrin Consulting, Nigeria
5. Centre for Rural Health, School of Nursing and Public Health, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa
6. TB PPM Learning Network, Research Institute of the McGill University Health Centre
7. Department of Epidemiology, Biostatistics and Occupational Health, McGill University
8. School of Public Health, University of the Western Cape, Bellville South Africa

Keywords: TB case-finding and treatment, COVID-19, access to healthcare, tuberculosis, diagnosis and treatment,

This commentary has been accepted for publication with *Healthcare: The Journal of Delivery Science and Innovation* in October 2020.

Introduction

The coronavirus disease 2019 (COVID-19) has emerged as a serious threat to global public health, demanding urgent action and causing unprecedented worldwide change in a short space of time (Ghebreyesus, 2020). This disease has devastated economies, infringed on individual freedoms, and taken an unprecedented toll on healthcare systems worldwide. As of 09 October 2020, over 37 million cases of COVID-19 have been reported in 214 countries and territories, resulting in over a million deaths (Worldometers, 2020). Against the backdrop of the COVID-19 pandemic lies an older, insidious disease with very high mortality. As of 2018, tuberculosis (TB) was the leading cause of death by a single infectious agent and remains a potent threat to millions of people around the world, with an estimated 10 million people infected and 1.5 million deaths (World Health Organization, 2019). With the arrival of COVID-19, many of the highest TB-burden countries are grappling with high caseloads of COVID-19, with severe repercussions on healthcare delivery (Shadmi et al., 2020, Bulled and Singer, 2020). We discuss the differences between the two pandemics at present, consider the potential impact of COVID-19 on TB case management, and explore the opportunities that the COVID-19 response presents for advancing TB prevention and control now and in future.

Like COVID-19, TB is spread through minute droplets produced through coughing or sneezing (Riley et al., 1959, Riley, 1957). Unlike COVID-19, TB is a bacterium which can progress to active disease soon after exposure or persist in a dormant form as latent TB infection (Parrish et al., 1998). The latter makes containment of TB particularly tricky, as there is currently no reliable test to determine who is most likely to progress to active disease, once infected (Matteelli et al., 2017). Despite decades of research there is no effective TB vaccine, leaving the principles of mitigation for active TB are left to public health measures similar to COVID-19, i.e. identify active cases early and trace their contacts to test for disease. The reproductive number for TB ranges from 0.24 in low-burden settings to 4.3 in high-burden settings (Ma et al., 2018), compared to 2-4 for SARS-CoV-2 (the pathogen responsible for COVID-19 disease), making SARS-CoV-2 more transmissible across settings (Liu et al., 2020b). While both diseases spread more often in crowded areas, SARS-CoV-2 has been shown to transmit from both pre-symptomatic and asymptomatic people and is also likely to transmit through fomites, unlike TB (ref). Additionally, the serial interval, the time between symptom onset of an infected person and that of an infected contact, is greater than 4 months in TB (Liu et al., 2020b), compared to 3-5 days for COVID-19 (Nishiura et al., 2020). These differences have necessitated a heightened public health response to the COVID-19 pandemic.

Other similarities between the two pandemics are demonstrated in the way they affect populations. Though TB occurs globally, the majority of morbidity and mortality occurs in low- and middle-income settings, largely due to resource limitations which hamper efforts to contain the disease. Africa and Asia account for 85% of the world's TB numbers, and it is the poorest of the poor who are more heavily affected due to poorer housing, challenges accessing adequate care, and other conditions that hamper the immune system (World Health Organization, 2019). Although TB outbreaks occur everywhere, available diagnosis and treatment ensure that people in richer countries mostly recover from the disease (World Health Organization, 2020, World Health Organization, 2019). COVID-19, with its current rate of spread, lack of treatment and natural immunity, is exploiting many of the same health, economic, and social inequities in Brazil, India, UK, South Africa, and the United States, that TB has been doing for centuries (Nicola et al., 2020, Raisi-Estabragh et al., 2020, Shadmi et al., 2020, Buheji et al., 2020). Even advanced economies in Europe and North America have been hit hard and are grappling with outbreaks that have caused significant morbidity and mortality, as well as major economic and social upheaval (Worldometers, 2020, OECD, 2020). The inadequate response to COVID-19 in many countries (e.g. the United States) highlights the need for political leadership with a science-led response, supported by solidarity with historically marginalized populations, and within an adequately funded public health system (Weible et al., 2020, Yamey and Gonsalves, 2020). Worldwide, COVID-19 has exposed gaps in health systems and been instrumental in galvanizing the urgency, political will, action and resources required to aggressively fight the pandemic in some countries. However, there have been documented inequities in how resources have been deployed and to what populations they have been directed (Cash and Patel, 2020, Pirtle, 2020).

Unlike for COVID-19, an effective oral treatment regimen is available to treat people with active TB, rendering them non-infectious after less than two weeks of treatment (Jindani et al., 1980, Dharmadhikari et al., 2014). Preventive therapy is also available, and the WHO now recommends its expanded usage beyond people with higher risk (Houben et al., 2016, Rangaka et al., 2015, WHO, 2020c). Despite the availability of treatment and preventive measures, TB still results in an estimated 1.5 million deaths every year (World Health Organization, 2019). Although 7 million cases of TB were diagnosed in 2018, an estimated 3 million were undiagnosed, and about 30% of those diagnosed remained untreated (World Health Organization, 2019).

Despite modest progress in global TB prevention and control efforts over the last two decades, finding millions of TB cases remains a significant challenge. Unless these people are found and successfully treated, onward transmission of TB disease cannot be interrupted, and the centuries-old epidemic will continue unabated. The latest statistics indicate that current efforts are not enough to meet global TB elimination targets by 2030 (World Health Organization, 2019). We also note that the prioritization of resources to fight the COVID-19 pandemic and the increased danger of co-infection with SARS-CoV-2 to those with TB pose additional threats to TB control efforts (Liu et al., 2020a). As Pai warns, if concerns are not addressed, COVID-19 could substantially reverse gains in TB control and worsen the epidemic in the coming months (Pai, 2020b, Pai, 2020a). Early reports from several high-burden settings confirm these concerns (Pai, 2020b, Pang et al., Boffa et al., 2020). Recent modelling studies have also quantified excess TB infections and deaths due to COVID-19 disruptions in health services, with an estimated 10-16% increases in current rates (Glaziou, 2020, Hogan et al., 2020, StopTB Partnership, 2020, McQuaid et al., 2020, Cilloni et al., 2020).

Potential threats to TB care

In addition to the far-reaching impacts of COVID-19 on global economic, social, financial, political and health systems and the higher risk of poor outcomes for those with TB and other health conditions (Bigio J, 2020, Sands, 2020a), a lack of comprehensive disaster preparedness will result in specific impacts on TB case-finding and treatment access, outcomes and socioeconomic harms in low-resource settings.

Reduced access to healthcare

In line with World Health Organization recommendations, many countries are implementing directives to limit social contact in a bid to delay transmission and minimize the impact of COVID-

19 on healthcare provision. This typically involves compulsory lockdowns, which were also enforced in many high-burden TB countries, restriction of movement and disruption of routine activities. Movement restrictions are likely to interrupt access to health facilities and disrupt delivery of TB services such as community-based active case-finding, contact tracing, sputum transportation and distribution of essential commodities, even as the potential for community transmission increases (Bhargava and Shewade, 2020). Additionally, in many settings, TB patients are required to go to a health centre daily for directly observed therapy, which would be near impossible in a lock-down scenario. Thus, COVID-19 disruptions affect the TB service delivery system more than for most other conditions (Stop TB Indonesia, 2020, Jain et al., 2020).

These disruptions could also lead to possible drug stock-outs or expiries of laboratory reagents and other supplies.

Diversion of resources away from TB

Diversion of human resource, funding, and infrastructure towards COVID-19 will mean that routine provision of basic healthcare services is deprioritized. This can be expected to worsen as the intensity of the outbreak overwhelms health systems. Many high-TB burden countries are already showing steep increases in COVID-19 cases ((JHU), 2020), a trend likely to worsen as the pandemic progresses. The need for social distancing within health facilities has also meant limitations to the number of patients who can be seen daily at TB clinics in high-burden settings. In addition to being resource-limited, these countries typically have higher-risk populations and weaker health systems. A serious outbreak could lead to a significant increase in the number of missing TB cases and potentially set back recent progress in TB control.

Increased stigma

Stigma and fear of community discrimination associated with COVID-19 may deter access to care for patients with cough symptoms for the foreseeable future. Consequently, one can anticipate delays in care seeking and/or a reduction in the number of people with undiagnosed TB presenting to healthcare facilities. Patients may avoid seeking TB services for fear of contracting COVID-19. Healthcare workers may stigmatize patients with cough for fear of

COVID-19, especially in settings where personal protective equipment supply is inadequate. This will worsen the widely documented stigma that many TB patients face, and further delay care-seeking (de Vries et al., 2017, Rood et al., 2017, Getnet et al., 2017, Macintyre et al., 2017).

Catastrophic economic impacts on those at highest risk

The COVID-19 pandemic has already begun to devastate the global economy, with declines in economic activity around the global transportation of goods and services and widespread unemployment from lockdowns. The effect will be disproportionately borne by the poor who live hand to mouth. With little or no social safety net in many of the countries grappling with TB, HIV and malaria epidemics, further intensification of predisposing factors such as malnutrition, poverty and overcrowding can be expected. These conditions increase the risk of TB transmission leading to a spike in TB cases, further compounding the diagnostic and treatment access constraints already discussed.

TB care lessons and opportunities in the COVID-19 era

Despite the challenge that the COVID-19 pandemic poses to TB control, several opportunities exist which must be leveraged to mitigate threats and save lives. These include:

Resource availability and political priority

The COVID-19 pandemic has galvanized public health actions at global and country levels. Many countries, including those with limited health budgets, have made resources and infrastructure available at record speed in response to or in anticipation of a COVID-19 outbreak. The search for a vaccine and treatment for the virus is advancing at an extraordinary speed. The response has sometimes resulted in collaborations between governments, donors, private sector, non-government organizations, private citizens and other stakeholders. Global and national public health efforts are receiving a multisectoral response. This is an opportunity to also reiterate the TB agenda on national levels but will be challenging during the crisis.

Galvanizing action to address the social determinants of health

The pandemic has highlighted historic inequities in health access, especially for marginalized populations, which have been the fault lines of infectious disease transmission for centuries. Now, perhaps more than ever, lies the need to pragmatically address these social determinants of health, including poverty, economic, social and gender inequity, and malnutrition. Indeed, the COVID-19 response could enable countries to build resilient and equitable health systems and address the social determinants of health in tangible ways, and thus achieve a double dividend for epidemic control for TB, COVID-19, and future pandemics.

Mitigating the impact on health services

Even though, by definition, the emergency response to a pandemic requires prioritization above routine activities, vertical programming must be avoided where possible and care must be taken to avoid disabling other essential services. The West Africa Ebola epidemic of 2014, for example, led to widespread disruption of healthcare services including immunization services and a corresponding increase in under-five and maternal mortality in Liberia, Sierra Leone and Guinea (Matteelli et al., 2017, Elston et al., 2017). Similar outcomes can be avoided using several strategies including contextualized country plans, fundraising and sustained advocacy, trained and appropriately resourced health worker work force, personal protective equipment, critical care capacity, diagnostic laboratories, and resilient supply chain management systems (Pai, 2020b, Leach, 2020, Maffioli, 2020).

Opportunities to integrate COVID-19 services with other essential services

The similarities in COVID-19 and TB symptoms, particularly cough and fever, present an opportunity for service integration. Identifying active TB disease amongst COVID-19 patients and vice versa will be imperative to reduce severity of disease. Integration of testing will also improve TB case-finding. Cepheid received US FDA emergency use authorization in March 2020 for its new Xpert® Xpress COVID-19 diagnostic that can be processed on the GeneXpert platforms. This could fill a crucial diagnostic need, especially in low and middle-income countries (LMICs), many of which have an extensive network of GeneXpert machines for TB. In the same vein, the emergency infrastructure set up for the purpose of responding to the COVID pandemic can be absorbed by TB programs when the present pandemic has been quelled.

The role of public health communication in shaping public discourse and global action

Several studies have identified contributory factors for TB underdiagnosis, including stigma, poor disease knowledge and perception of healthcare services on the patient level, and lack of resources and poor knowledge of TB guidelines at the provider level (de Vries et al., 2017, Fuge et al., 2018, Tomás et al., 2013, Oga-Omenka et al., 2020c). To mitigate these, technological solutions such as e-health and telemedicine have been successfully employed in new and innovative ways. Large scale mass media campaigns have been launched and social media have been exploited in some settings to quell misinformation and educate the public, emphasizing trusted scientific sources, although this has been the reverse in some countries. There are lessons to be carried forward in TB elimination, such as the innovative use of telehealth, text messaging and use of social media as well as the engagement of celebrities, journalists and popular news sources for the mass proliferation of correct information and to unite people experiencing the challenges of social distancing. As it could be challenging to disseminate correct public health information through social media, there is a need to develop and deploy more scientifically based behaviour change communication.

COVID-19 has disproportionately affected marginalized populations in high-income countries to date, and its continuous spread within LMICs presents a real and present concern to vulnerable populations, even more so for those in high-TB burden countries. The COVID-19 response to date has demonstrated that, with the right amount of political will, prioritization and investments, it is possible for the international community to mobilize resources, accelerate scientific discovery, and deploy new public health tools to fight a pandemic. These same strategies can thus be employed for TB. Given that most people who develop TB can be cured with timely diagnosis and correct treatment, a moral imperative exists to once and for all end the significant yet needless morbidity and mortality resulting from TB (Sands, 2020b). The momentum in global attention, investment and priority to public health must be galvanized to end TB and other health threats for all people around the world.

"In the rush to return back to normal, use this time to consider which parts of normal are worth rushing back to". - Lawrence H. Gerstein, Ph.D.

REFERENCES

(JHU), J. H. U. 2020. *Coronavirus COVID-19 Global Cases* [Online]. Center for Systems Science and Engineering (CSSE), Johns Hopkins University (JHU). Available: https://coronavirus.jhu.edu/map.html [Accessed 31 March 2020 2020].

ABEGAZ, T. M., SHEHAB, A., GEBREYOHANNES, E. A., BHAGAVATHULA, A. S. & ELNOUR, A. A. 2017. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. *Medicine,* 96.

ABIDI, S., ACHAR, J., NEINO, M. M. A., BANG, D., BENEDETTI, A., BRODE, S., CAMPBELL, J. R., CASAS, E. C., CONRADIE, F. & DRAVNIECE, G. 2020. Standardised shorter regimens versus individualised longer regimens for rifampin-or multidrug-resistant tuberculosis. *European Respiratory Journal,* 55.

ABIMBOLA, S., UKWAJA, K. N., ONYEDUM, C. C., NEGIN, J., JAN, S. & MARTINIUK, A. L. 2015. Transaction costs of access to health care: Implications of the care-seeking pathways of tuberculosis patients for health system governance in Nigeria. *Global Public Health,* 10**,** 1060-1077.

ADAY, L. A. & ANDERSEN, R. 1974. A framework for the study of access to medical care. *Health services research,* 9**,** 208.

ADEBISI, Y. A., AGUMAGE, I., SYLVANUS, T. D., NAWAILA, I. J., EKWERE, W. A., NASIRU, M., OKON, E. E., EKPENYONG, A. M. & LUCERO-PRISNO III, D. E. 2020. Burden of tuberculosis and challenges facing its eradication in West Africa. *target,* 4.

ADEJUMO, O. A., DANIEL, O. J., ADEPOJU, V. A., FEMI-ADEBAYO, T., ADEBAYO, B. I. & AIRAUHI, A. O. 2020. Challenges of Tuberculosis Control in Lagos State, Nigeria: A Qualitative Study of Health-Care Providers' Perspectives. *Niger Med J,* 61**,** 37-41.

ADEYEMO, O. O. & OSOFISAN, A. O. 2012. Empirical Study of Statistical Based Method and Artificial Neural Networks for Credit Rating in Nigerian Banks. *Science,* 3.

AJAYI, I. O., JEGEDE, A. S., FALADE, C. O. & SOMMERFELD, J. 2013. Assessing resources for implementing a community directed intervention (CDI) strategy in delivering multiple health interventions in urban poor communities in Southwestern Nigeria: a qualitative study. *Infectious diseases of poverty,* 2**,** 25.

ALBANNA, A. S. & MENZIES, D. 2011. Drug-Resistant Tuberculosis. *Drugs,* 71**,** 815-825.

ALMGREN, G. 2018. *Health care politics, policy, and services: a social justice analysis*, Springer publishing company.

AMBE, G., LÖNNROTH, K., DHOLAKIA, Y., COPREAUX, J., ZIGNOL, M., BORREMANS, N. & UPLEKAR, M. 2005. Every provider counts: effect of a comprehensive public-private mix approach for TB control in a large metropolitan area in India. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 562-568.

ANDERSEN, R. & NEWMAN, J. F. 2005. Societal and individual determinants of medical care utilization in the United States. *The Milbank Quarterly,* 83**,** Online-only-Online-only.

ANDERSEN, R. M., MCCUTCHEON, A., ADAY, L. A., CHIU, G. Y. & BELL, R. 1983. Exploring dimensions of access to medical care. *Health services research,* 18**,** 49.

ANDREWS, J. R., BASU, S., DOWDY, D. W. & MURRAY, M. B. 2015. The epidemiological advantage of preferential targeting of tuberculosis control at the poor. *The International Journal of Tuberculosis and Lung Disease,* 19**,** 375-380.

ANYANWU, J. C. 2005. Rural poverty in Nigeria: Profile, determinants and exit paths. *African Development Review,* 17**,** 435-460.

ARGY, O. 1996. Standards of care. *JAMA,* 275**,** 1296-1296.

ASUZU, M. C. 2004. Commentary: The necessity for a health systems reform in Nigeria. *Journal of community medicine and primary health care,* 16**,** 1-3.

AWOFESO, N. 2008. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis treatment. *Bulletin of the World health Organization,* 86**,** B-D.

BABATUNDE, O. I., BISMARK, E. C., AMAECHI, N. E., GABRIEL, E. I. & OLANIKE, A.-U. R. 2015. Determinants of treatment delays among pulmonary tuberculosis patients in Enugu Metropolis, South-East, Nigeria. *Health,* 7**,** 1506.

BAILIE, J., SCHIERHOUT, G., LAYCOCK, A., KELAHER, M., PERCIVAL, N., O'DONOGHUE, L., MCNEAIR, T. & BAILIE, R. 2015. Determinants of access to chronic illness care: a mixed-methods evaluation of a national multifaceted chronic disease package for Indigenous Australians. *BMJ open,* 5**,** e008103.

BANK., W. 2017. *Current health expenditure (% GDP)* [Online]. Available: https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?contextual=max&locations=ZG-1W [Accessed].

BARKER, K. & SABIDO, M. 2005. *Soap Operas for Social Change to Prevent HIV/AIDs: A training guide for journalists and media personnel*, Population Media Center.

BARNETT-PAGE, E. & THOMAS, J. 2009. Methods for the synthesis of qualitative research: a critical review. *BMC medical research methodology,* 9**,** 1-11.

BARRATT, H., CAMPBELL, M., MOORE, L., ZWARENSTEIN, M. & BOWER, P. 2016. Challenges, solutions and future directions in the evaluation of service innovations in health care and public health. *Health Services and Delivery Research,* 4.

BASU, S., FRIEDLAND, G. H., MEDLOCK, J., ANDREWS, J. R., SHAH, N. S., GANDHI, N. R., MOLL, A., MOODLEY, P., STURM, A. W. & GALVANI, A. P. 2009. Averting epidemics of extensively drug-resistant tuberculosis. *Proceedings of the National Academy of Sciences of the United States of America,* 106**,** 7672-7677.

BELARD, S., JANSSEN, S., OSBAK, K. K., ADEGNIKA, A. A., ONDOUNDA, M. & GROBUSCH, M. P. 2015. Limited access to drugs for resistant tuberculosis: a call to action. *Journal of Public Health,* 37**,** 691-693.

BEYELER, N., LIU, J. & SIEVERDING, M. 2015. A systematic review of the role of proprietary and patent medicine vendors in healthcare provision in Nigeria. *PLoS One,* 10.

BHARGAVA, A. & SHEWADE, H. D. 2020. The potential impact of the COVID-19 response related lockdown on TB incidence and mortality in India. *Indian Journal of Tuberculosis*.

BHUTTA, Z. A., SALAM, R. A., DAS, J. K. & LASSI, Z. S. 2014a. Tackling the existing burden of infectious diseases in the developing world: existing gaps and the way forward. *Infectious diseases of poverty,* 3**,** 1.

BHUTTA, Z. A., SOMMERFELD, J., LASSI, Z., SALAM, R. A. & DAS, J. K. 2014b. Global burden, distribution, and interventions for infectious diseases of poverty.

BIADGLEGNE, F., SACK, U. & RODLOFF, A. C. 2014. Multidrug-resistant tuberculosis in Ethiopia: Efforts to expand diagnostic services, treatment and care. *Antimicrobial Resistance and Infection Control,* 3.

BIEH, K. L., WEIGEL, R. & SMITH, H. 2017a. Hospitalized care for MDR-TB in Port Harcourt, Nigeria: a qualitative study. *BMC Infect Dis,* 17**,** 50.

BIEH, K. L., WEIGEL, R. & SMITH, H. 2017b. Hospitalized care for MDR-TB in Port Harcourt, Nigeria: a qualitative study. *BMC infectious diseases,* 17**,** 1-9.

BIGIO J, P. M. 2020. *How Covid is making it tougher to tackle TB, AIDS, malaria and child health* [Online]. The Print. Available: https://theprint.in/health/how-covid-is-making-it-tougher-to-tackle-tb-aids-malaria-and-child-health/443658/ [Accessed].

BOFFA, J., MHLABA, T., SULIS, G., MOYO, S., SIFUMBA, Z., PAI, M., DAFTARY, A. & FARHAM, B. 2020. COVID-19 and tuberculosis in South Africa: A dangerous combination. *South African Medical Journal,* 110**,** 1.

BOYD, R., FORD, N., PADGEN, P. & COX, H. 2017. Time to treatment for rifampicin-resistant tuberculosis: systematic review and meta-analysis. *The International Journal of Tuberculosis and Lung Disease,* 21**,** 1173-1180.

BRAVEMAN, P. A. 2003. Monitoring equity in health and healthcare: a conceptual framework. *Journal of health, population and nutrition***,** 181-192.

BRAVEMAN, P. A., KUMANYIKA, S., FIELDING, J., LAVEIST, T., BORRELL, L. N., MANDERSCHEID, R. & TROUTMAN, A. 2011. Health disparities and health equity: the issue is justice. *American journal of public health,* 101**,** S149-S155.

BUHEJI, M., DA COSTA CUNHA, K., BEKA, G., MAVRIC, B., DE SOUZA, Y., DA COSTA SILVA, S. S., HANAFI, M. & YEIN, T. C. 2020. The extent of covid-19 pandemic socio-economic impact on global poverty. a global integrative multidisciplinary review. *American Journal of Economics,* 10**,** 213-224.

BULLED, N. & SINGER, M. 2020. In the shadow of HIV & TB: A commentary on the COVID epidemic in South Africa. *Global Public Health***,** 1-13.

CAMBANIS, A., RAMSAY, A., YASSIN, M. A. & CUEVAS, L. E. 2007. Duration and associated factors of patient delay during tuberculosis screening in rural Cameroon. *Tropical Medicine & International Health,* 12**,** 1309-1314.

CASH, R. & PATEL, V. 2020. Has COVID-19 subverted global health? *The Lancet,* 395**,** 1687-1688.

CAZABON, D., ALSDURF, H., SATYANARAYANA, S., NATHAVITHARANA, R., SUBBARAMAN, R., DAFTARY, A. & PAI, M. 2017a. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. *International Journal of Infectious Diseases,* 56**,** 111-116.

CAZABON, D., SURESH, A., OGHOR, C., QIN, Z. Z., KIK, S. V., DENKINGER, C. M. & PAI, M. 2017b. Implementation of Xpert MTB/RIF in 22 high tuberculosis burden countries: are we making progress? *European Respiratory Journal,* 50.

CHILESHE, M. & BOND, V. A. 2010. Barriers and outcomes: TB patients co-infected with HIV accessing antiretroviral therapy in rural Zambia.

CHIMBINDI, N., BOR, J., NEWELL, M. L. & TANSER…, F. 2015. Time and money: the true costs of health care utilization for patients receiving "free" HIV/tuberculosis care and treatment in rural KwaZulu-Natal.

CILLONI, L., FU, H., VESGA, J. F., DOWDY, D., PRETORIUS, C., AHMEDOV, S., NAIR, S. A., MOSNEAGA, A., MASINI, E. O. & SUVANAND, S. 2020. The potential impact of the COVID-19 pandemic on tuberculosis: a modelling analysis. *medRxiv*.

CLIFFORD, B. K., MIZRAHI, D., SANDLER, C. X., BARRY, B. K., SIMAR, D., WAKEFIELD, C. E. & GOLDSTEIN, D. 2018. Barriers and facilitators of exercise experienced by cancer survivors: a mixed methods systematic review. *Supportive Care in Cancer,* 26**,** 685-700.

COLVIN, C., MUGYABUSO, J., MUNUO, G., LYIMO, J., OREN, E., MKOMWA, Z., MAKAME, M., MWANGOMALE, A., MAHAMBA, V. & MUELLER, L. 2014. Evaluation of community-based interventions to improve TB case detection in a rural district of Tanzania. *Global Health: Science and Practice,* 2**,** 219-225.

COMMITTEE ON QUALITY OF HEALTH CARE IN AMERICA, I. O. M. 2001. Crossing the quality chasm: a new health system for the 21st century. *An Institute of Medicine Report*.

COOKE, A., SMITH, D. & BOOTH, A. 2012. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qualitative health research,* 22**,** 1435-1443.

CORBETT, E. L., BANDASON, T., DUONG, T., DAUYA, E., MAKAMURE, B., CHURCHYARD, G. J., WILLIAMS, B. G., MUNYATI, S. S., BUTTERWORTH, A. E. & MASON, P. R. 2010. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *The Lancet,* 376**,** 1244-1253.

CORRIGAN, J. M. 2005. Crossing the quality chasm. *Building a better delivery system*.

COX, H., DICKSON-HALL, L., NDJEKA, N., VAN'T HOOG, A., GRANT, A., COBELENS, F., STEVENS, W., NICOL, M. & VAN'T HOOG, A. 2017. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study. *PLoS Medicine,* 14**,** 1-19.

COX, H., HUGHES, J., DANIELS, J., AZEVEDO, V., MCDERMID, C., POOLMAN, M., BOULLE, A., GOEMAERE, E. & VAN CUTSEM, G. 2014. Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *The International Journal of Tuberculosis and Lung Disease,* 18**,** 441-448.

COX, H. S., DANIELS, J. F., MULLER, O., NICOL, M. P., COX, V., VAN CUTSEM, G., MOYO, S., DE AZEVEDO, V. & HUGHES, J. 2015. Impact of Decentralized Care and the Xpert MTB/RIF Test on Rifampicin-Resistant Tuberculosis Treatment Initiation in Khayelitsha, South Africa. *Open Forum Infectious Diseases,* 2.

CRESWELL, J. W. 1998. Qualitative inquiry and research design: Choosing among five designs. Thousand Oaks, CA: Sage.

CRESWELL, J. W. 2013. *Research design: Qualitative, quantitative, and mixed methods approaches*, Sage publications.

CRESWELL, J. W. & CLARK, V. L. P. 2007. Designing and conducting mixed methods research.

CRESWELL, J. W., CLARK, V. P. & GARRETT, A. 2003. Advanced mixed methods research. *Handbook of mixed methods in social and behavioural research. Thousand Oaks, CA: Sage***,** 209-240.

CRESWELL, J. W. & PLANO CLARK, V. L. 2011. Choosing a mixed methods design. *Designing and conducting mixed methods research,* 2**,** 53-106.

CRUZES, D. S. & DYBA, T. Recommended steps for thematic synthesis in software engineering. 2011 International Symposium on Empirical Software Engineering and Measurement, 2011. IEEE, 275-284.

CSDH 2008. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva: World Health Organization.

DATIKO, D. G. & LINDTJØRN, B. 2009. Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. *PloS one,* 4**,** e5443.

DE VRIES, S. G., CREMERS, A. L., HEUVELINGS, C. C., GREVE, P. F., VISSER, B. J., BÉLARD, S., JANSSEN, S., SPIJKER, R., SHAW, B. & HILL, R. A. 2017. Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. *The Lancet Infectious Diseases,* 17**,** e128-e143.

DESHMUKH, R. D., DHANDE, D., SACHDEVA, K. S., SREENIVAS, A., KUMAR, A., SATYANARAYANA, S., PARMAR, M., MOONAN, P. K. & LO, T. Q. 2015. Patient and provider reported reasons for lost to follow up in MDRTB treatment: a qualitative study from a drug resistant TB Centre in India. *PLoS One,* 10.

DHARMADHIKARI, A. S., MPHAHLELE, M., VENTER, K., STOLTZ, A., MATHEBULA, R., MASOTLA, T., VAN DER WALT, M., PAGANO, M., JENSEN, P. & NARDELL, E. 2014. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease,* 18**,** 1019-1025.

DLAMINI-MVELASE, N. R., WERNER, L., PHILI, R., CELE, L. P. & MLISANA, K. P. 2014. Effects of introducing Xpert MTB/RIF test on multi-drug resistant tuberculosis diagnosis in KwaZulu-Natal South Africa. *BMC Infectious Diseases,* 14.

DOULLA, B. E., SQUIRE, S. B., MACPHERSON, E., NGADAYA, E. S., MUTAYOBA, B. K. & LANGLEY, I. 2019. Routine surveillance for the identification of drug resistant Tuberculosis in Tanzania: A cross-sectional study of stakeholders' perceptions. *PloS one,* 14**,** e0212421.

DUTTON, D. 1986. Financial, organizational and professional factors affecting health care utilization. *Social science & medicine,* 23**,** 721-735.

EBONWU, J. I., TINT, K. S. & IHEKWEAZU, C. 2013. Low treatment initiation rates among multidrug-resistant tuberculosis patients in Gauteng, South Africa, 2011. *International Journal of Tuberculosis and Lung Disease,* 17**,** 1043-1048.

ELSTON, J., CARTWRIGHT, C., NDUMBI, P. & WRIGHT, J. 2017. The health impact of the 2014–15 Ebola outbreak. *Public Health,* 143**,** 60-70.

ENGEL, N., DAVIDS, M., BLANKVOORT, N., PAI, N. P., DHEDA, K. & PAI, M. 2015. Compounding diagnostic delays: A qualitative study of point-of-care testing in South Africa. *Tropical Medicine and International Health,* 20**,** 493-500.

ENGEL, N. & PAI, M. 2013. Tuberculosis diagnostics: why we need more qualitative research. *Journal of epidemiology and global health,* 3**,** 119-121.

ERAH, P. & OJIEABU, W. 2009. Success of the control of tuberculosis in Nigeria: A Review. *International Journal of Health Research,* 2.

ERWIN, E. J., BROTHERSON, M. J. & SUMMERS, J. A. 2011. Understanding qualitative metasynthesis: Issues and opportunities in early childhood intervention research. *Journal of Early Intervention,* 33**,** 186-200.

ETTEHAD, D., SCHAAF, H. S., SEDDON, J. A., COOKE, G. S. & FORD, N. 2012. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infectious Diseases,* 12**,** 449-456.

EUI 2019. It's Time to End Drug-Resistant Tuberculosis: The case for action. The Economist Intelligence Unit Limited.

EVANS, D., SINEKE, T., SCHNIPPEL, K., BERHANU, R., GOVATHSON, C., BLACK, A., LONG, L. & ROSEN, S. 2018. Impact of Xpert MTB/RIF and decentralized care on linkage to care and drug-resistant tuberculosis treatment outcomes in Johannesburg, South Africa. *BMC health services research,* 18**,** 973.

EVANS, D. B., HSU, J. & BOERMA, T. 2013. Universal health coverage and universal access. SciELO Public Health.

FALZON, D., JARAMILLO, E., WARES, F., ZIGNOL, M., FLOYD, K. & RAVIGLIONE, M. C. 2013. Universal access to care for multidrug-resistant tuberculosis: an analysis of surveillance data. *Lancet Infectious Diseases,* 13**,** 690-697.

FALZON, D., MIRZAYEV, F., WARES, F., BAENA, I. G., ZIGNOL, M., LINH, N., WEYER, K., JARAMILLO, E., FLOYD, K. & RAVIGLIONE, M. 2015. Multidrug-resistant tuberculosis around the world: what progress has been made? *European Respiratory Journal,* 45**,** 150-160.

FALZON, D., SCHÜNEMANN, H. J., HARAUSZ, E., GONZÁLEZ-ANGULO, L., LIENHARDT, C., JARAMILLO, E. & WEYER, K. 2017. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. *European Respiratory Journal,* 49**,** 1602308.

FARMER, P. 1996. Social inequalities and emerging infectious diseases. *Emerging infectious diseases,* 2**,** 259.

FARMER, P. E., NIZEYE, B., STULAC, S. & KESHAVJEE, S. 2006. Structural violence and clinical medicine. *PLoS Med,* 3**,** e449.

FEDERAL MINISTRY OF HEALTH, N. U. 2002. Women and children rights in Nigeria: A wake up call - Situation assessment and analysis. . *In:* FMOH (ed.). Abuja, Nigeria.

FILMER, D. & PRITCHETT, L. H. 2001. Estimating wealth effects without expenditure data—or tears: an application to educational enrollments in states of India. *Demography,* 38**,** 115-132.

FINNIE, R. K., KHOZA, L. B., VAN DEN BORNE, B., MABUNDA, T., ABOTCHIE, P. & MULLEN, P. D. 2011. Factors associated with patient and health care system delay in diagnosis and treatment for TB in sub-Saharan African countries with high burdens of TB and HIV. *Tropical medicine & international health,* 16**,** 394-411.

FLOYD, K., SKEVA, J., NYIRENDA, T., GAUSI, F. & SALANIPONI, F. 2003. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. *The International Journal of Tuberculosis and lung disease,* 7**,** S29-S37.

FMOH 2008. The National Guidelines for TB Infection Control. *In:* HEALTH, D. O. P. (ed.). Abuja, Nigeria.

FMOH 2012a. First National TB Prevalence Survey 2012. *Federal Ministry of Health Nigeria*.

FMOH 2012b. First National TB Prevalence Survey Nigeria 2012. *Federal Ministry of Health Nigeria*.

FOLBRE, N. 2014. Who cares. *A feminist critique of the care economy. Nueva York: Rosa Luxemburg Stiftung*.

FUGE, T. G., BAWORE, S. G., SOLOMON, D. W. & HEGANA, T. Y. 2018. Patient delay in seeking tuberculosis diagnosis and associated factors in Hadiya Zone, Southern Ethiopia. *BMC research notes,* 11**,** 115.

GALE, N. K., HEATH, G., CAMERON, E., RASHID, S. & REDWOOD, S. 2013. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC medical research methodology,* 13**,** 117.

GANDHI, N. R., NUNN, P., DHEDA, K., SCHAAF, H. S., ZIGNOL, M., VAN SOOLINGEN, D., JENSEN, P. & BAYONA, J. 2010a. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *The Lancet,* 375**,** 1830-1843.

GANDHI, N. R., SHAH, N. S., ANDREWS, J. R., VELLA, V., MOLL, A. P., SCOTT, M., WEISSMAN, D., MARRA, C., LALLOO, U. G. & FRIEDLAND, G. H. 2010b. HIV coinfection in multidrug-and extensively drug-resistant tuberculosis results in high early mortality. *American journal of respiratory and critical care medicine,* 181**,** 80-86.

GEHRE, F., OTU, J., KENDALL, L., FORSON, A., KWARA, A., KUDZAWU, S., KEHINDE, A. O., ADEBIYI, O., SALAKO, K. & BALDEH, I. 2016. The emerging threat of pre-extensively drug-resistant tuberculosis in West Africa: preparing for large-scale tuberculosis research and drug resistance surveillance. *BMC medicine,* 14**,** 160.

GETNET, F., DEMISSIE, M., ASSEFA, N., MENGISTIE, B. & WORKU, A. 2017. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis. *BMC pulmonary medicine,* 17**,** 202.

GFATM 2020. Global Fund Survey: Majority of HIV, TB and Malaria Programs Face Disruptions as a Result of COVID-19.

GHEBREYESUS, T. 2020. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020. *In:* WORLD HEALTH ORGANIZATION (ed.). World Health Organization,.

GIDADO, M., NWOKOYE, N., NWADIKE, P., AJIBOYE, P., ENEOGU, R., USENI, S., ONAZI, J., LAWANSON, A., ELOM, E. & TUBI, A. 2018. Unsuccessful Xpert® MTB/RIF results: the Nigerian experience. *Public health action,* 8**,** 2-6.

GIDADO, M., NWOKOYE, N., OGBUDEBE, C., NSA, B., NWADIKE, P., AJIBOYE, P., ENEOGU, R., USENI, S., ELOM, E. & LAWANSON, A. 2019. Assessment of GeneXpert MTB/RIF performance by type and level of health-care facilities in Nigeria. *Nigerian Medical Journal: Journal of the Nigeria Medical Association,* 60**,** 33.

GIDADO, M., ONAZI, O., OBASANYA, O., CHUKWUEME, N., ONAZI, M., OMONIYI, A. & ODUSOTE, T. 2014. Assessing the Effectiveness of Xpert MTB/RIF in the Diagnoses of TB Among HIV Smear Negative TB Patients in Nigeria. *Journal of Health Science,* 2**,** 145-51.

GILBERT, J. A., LONG, E. F., BROOKS, R. P., FRIEDLAND, G. H., MOLL, A. P., TOWNSEND, J. P., GALVANI, A. P. & SHENOI, S. V. 2015. Integrating community-based interventions to reverse the convergent TB/HIV epidemics in rural South Africa. *PLoS ONE,* 10.

GILSON, L. 2012. Health Policy and systems research A Methodology Reader. In. Geneva, Switzerland: Alliance for Health Policy and Systems Research. *World Health Organization*.

GLAZIOU, P. 2020. Predicted impact of the COVID-19 pandemic on global tuberculosis deaths in 2020. *medRxiv*.

GLAZIOU, P., SISMANIDIS, C., ZIGNOL, M. & FLOYD, K. 2016. Methods used by WHO to estimate the global burden of TB disease. *Global TB Programme, WHO, Geneva*.

GODDARD, M. & SMITH, P. 2001. Equity of access to health care services:: Theory and evidence from the UK. *Social science & medicine,* 53**,** 1149-1162.

GOLD, M. 1998. Beyond coverage and supply: measuring access to healthcare in today's market. *Health Services Research,* 33**,** 625.

GOLDEN, S. D. & EARP, J. A. L. 2012. Social ecological approaches to individuals and their contexts: twenty years of health education & behavior health promotion interventions. *Health education & behavior,* 39**,** 364-372.

GOLUB, J., MOHAN, C., COMSTOCK, G. & CHAISSON, R. 2005a. Active case finding of tuberculosis: historical perspective and future prospects. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease,* 9**,** 1183.

GOLUB, J. E., MOHAN, C., COMSTOCK, G. & CHAISSON, R. 2005b. Active case finding of tuberculosis: historical perspective and future prospects. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 1183-1203.

GOPICHANDRAN, V., ROY, P. & SITARAM, A. 2010. Impact of a simple educational intervention on the knowledge and awareness of tuberculosis among high school children in Vellore, India. *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine,* 35**,** 174.

GULLIFORD, M., FIGUEROA-MUNOZ, J., MORGAN, M., HUGHES, D., GIBSON, B., BEECH, R. & HUDSON, M. 2002. What does' access to health care'mean? *Journal of health services research & policy,* 7**,** 186-188.

GUPTA-WRIGHT, A., TOMLINSON, G. S., RANGAKA, M. X. & FLETCHER, H. A. 2018. World TB Day 2018: The Challenge of Drug Resistant Tuberculosis. *F1000Research,* 7.

GWATKIN, D. R., BHUIYA, A. & VICTORA, C. G. 2004. Making health systems more equitable. *The Lancet,* 364**,** 1273-1280.

HABER, N., PILLAY, D., PORTER, K. & BÄRNIGHAUSEN, T. 2016. Constructing the cascade of HIV care: methods for measurement. *Current Opinion in HIV and AIDS,* 11**,** 102-108.

HANKIVSKY, O. 2012. Women's health, men's health, and gender and health: Implications of intersectionality. *Social science & medicine,* 74**,** 1712-1720.

HANRAHAN, C. F., DORMAN, S. E., ERASMUS, L., KOORNHOF, H., COETZEE, G. & GOLUB, J. E. 2012. The impact of expanded testing for multidrug resistant tuberculosis using geontype MTBDRplus in South Africa: an observational cohort study. *PloS one,* 7**,** e49898.

HANRAHAN, C. F., SELIBAS, K., DEERY, C. B., DANSEY, H., CLOUSE, K., BASSETT, J., SCOTT, L., STEVENS, W., SANNE, I. & VAN RIE, A. 2013. Time to Treatment and Patient Outcomes among TB Suspects Screened by a Single Point-of-Care Xpert MTB/RIF at a Primary Care Clinic in Johannesburg, South Africa. *Plos One,* 8.

HARGREAVES, J. R., BOCCIA, D., EVANS, C. A., ADATO, M., PETTICREW, M. & PORTER, J. D. 2011. The social determinants of tuberculosis: from evidence to action. *American journal of public health,* 101**,** 654-662.

HASSAN, A., OLUKOLADE, R., OGBUJI, Q., AFOLABI, S., OKWUONYE, L., KUSIMO, O., OSHO, J., OSINOWO, K. & LADIPO, O. 2017. Knowledge about tuberculosis: a precursor to effective TB control—findings from a follow-up national KAP study on tuberculosis among Nigerians. *Tuberculosis research and treatment,* 2017.

HASSAN, R. M. & BABU, S. C. 1991. Measurement and determinants of rural poverty: Household consumption patterns and food poverty in rural Sudan. *Food policy,* 16**,** 451-460.

HAYES, T. & DELK, R. 2018. Understanding the Social Determinants of Health.; 2018.

HELLER, T., LESSELLS, R. J., WALLRAUCH, C. G., BARNIGHAUSEN, T., COOKE, G. S., MHLONGO, L., MASTER, I. & NEWELL, M. L. 2010. Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. *International Journal of Tuberculosis & Lung Disease,* 14**,** 420-6.

HIGGINS, J. P. 2008. Cochrane handbook for systematic reviews of interventions version 5.0. 1. The Cochrane Collaboration. *http://www. cochrane-handbook. org*.

HODKINSON, P. & HODKINSON, H. The strengths and limitations of case study research. learning and skills development agency conference at Cambridge, 2001. 5-7.

HOGAN, A. B., JEWELL, B., SHERRARD-SMITH, E., VESGA, J., WATSON, O. J., WHITTAKER, C., HAMLET, A., SMITH, J., AINSLIE, K. & BAGUELIN, M. 2020. The potential impact of the COVID-19 epidemic on HIV, TB and Malaria in low-and middle-income countries. *Imperial College London (01-05-2020) DOI: https://doi. org/10.25561/78670*.

HONG, Q. N., PLUYE, P., FÀBREGUES, S., BARTLETT, G., BOARDMAN, F., CARGO, M., DAGENAIS, P., GAGNON, M.-P., GRIFFITHS, F. & NICOLAU, B. 2018. Mixed methods appraisal tool (MMAT), version 2018. *Registration of copyright,* 1148552.

HOUBEN, R. M., MENZIES, N. A., SUMNER, T., HUYNH, G. H., ARINAMINPATHY, N., GOLDHABER-FIEBERT, J. D., LIN, H.-H., WU, C.-Y., MANDAL, S. & PANDEY, S. 2016. Feasibility of achieving the 2025 WHO global tuberculosis targets in South Africa, China, and India: a combined analysis of 11 mathematical models. *The Lancet Global Health,* 4**,** e806-e815.

HUDELSON, P. 1996. Gender differentials in tuberculosis: the role of socio-economic and cultural factors. *Tubercle and lung disease,* 77**,** 391-400.

HUFF-ROUSSELLE, M. 2013. Reflections on the frameworks we use to capture complex and dynamic health sector issues. *The International journal of health planning and management,* 28**,** 95-101.

IBRAHIM, L. M., HADEJIA, I. S., NGUKU, P., DANKOLI, R., WAZIRI, N. E., AKHIMIEN, M. O., OGIRI, S., OYEMAKINDE, A., DALHATU, I. & NWANYANWU, O. 2014a. Factors associated with interruption of treatment among Pulmonary Tuberculosis patients in Plateau State, Nigeria. 2011. *Pan African Medical Journal,* 17.

IBRAHIM, L. M., HADEJIA, I. S., NGUKU, P., DANKOLI, R., WAZIRI, N. E., AKHIMIEN, M. O., OGIRI, S., OYEMAKINDE, A., DALHATU, I., NWANYANWU, O. & NSUBUGA, P. 2014b. Factors associated with interruption of treatment among Pulmonary Tuberculosis patients in Plateau State, Nigeria. 2011. *The Pan African medical journal,* 17**,** 78.

INSTITUTE OF HUMAN VIROLOGY NIGERIA 2017. DR-TB COUGH TO CURE – WHAT WE NEED TO KNOW.

INTERNATIONAL MONETARY FUND. 2019. *Gross domestic product per capita.* [Online]. Available: https://www.imf.org/external/pubs/ft/weo/2019/02/weodata/index.aspx [Accessed 03 May 2020 2020].

IRUEDO, J., O'MAHONY, D., MABUNDA, S., WRIGHT, G. & CAWE, B. 2017. The effect of the Xpert MTB/RIF test on the time to MDR-TB treatment initiation in a rural setting: a cohort study in South Africa's Eastern Cape Province. *BMC Infectious Diseases,* 17**,** 1-9.

ISLAM, Z., SANIN, K. I. & AHMED, T. 2017. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation research. *BMC public health,* 17**,** 131.

IVANKOVA, N. V., CRESWELL, J. W. & STICK, S. L. 2006. Using mixed-methods sequential explanatory design: From theory to practice. *Field methods,* 18**,** 3-20.

IYALOMHE, G. B. & IYALOMHE, S. I. 2012. Health seeking behavior of rural dwellers in Southern Nigeria: Implications for healthcare professionals. *Int J Trop Dis Health,* 2**,** 62-71.

JACOBSON, K. R., BARNARD, M., KLEINMAN, M. B., STREICHER, E. M., RAGAN, E. J., WHITE, L. F., SHAPIRA, O., DOLBY, T., SIMPSON, J. & SCOTT, L. 2017. Implications of failure to routinely diagnose resistance to second-line drugs in patients with rifampicin-resistant tuberculosis on Xpert MTB/RIF: a multisite observational study. *Clinical Infectious Diseases,* 64**,** 1502-1508.

JACOBSON, K. R., THERON, D., KENDALL, E. A., FRANKE, M. F., BARNARD, M., VAN HELDEN, P. D., VICTOR, T. C., STREICHER, E. M., MURRAY, M. B. & WARREN, R. M. 2012. Implementation of GenoType MTBDR plus Reduces Time to Multidrug-Resistant Tuberculosis Therapy Initiation in South Africa. *Clinical infectious diseases,* 56**,** 503-508.

JAIN, V. K., IYENGAR, K. P., SAMY, D. A. & VAISHYA, R. 2020. Tuberculosis in the era of COVID-19 in India. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*.

JINDANI, A., ABER, V., EDWARDS, E. & MITCHISON, D. 1980. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *American Review of Respiratory Disease,* 121**,** 939-949.

JOKWIRO, A., TIMIRE, C., HARRIES, A., GWINJI, P., MULEMA, A., TAKARINDA, K., MAFAUNE, P. & SANDY, C. 2018. Has the utilisation of Xpert® MTB/RIF in Manicaland Province, Zimbabwe, improved with new guidance on whom to test? *Public health action,* 8**,** 124-129.

JOMBO, G. & MBAAVE, P. T. 2018. Global Tuberculosis Burden: Is Nigeria Losing The War? *Journal of BioMedical Research and Clinical Practice,* 1**,** ix-xi.

KALIAKBAROVA, G., PAK, S., ZHAKSYLYKOVA, N., RAIMOVA, G., TEMERBEKOVA, B. & HOF, S. 2013. Psychosocial support improves treatment adherence among MDR-TB patients: experience from East Kazakhstan. *The Open Infectious Diseases Journal,* 7.

KARAMAGI, E., SENSALIRE, S., MUHIRE, M., KISAMBA, H., BYABAGAMBI, J., RAHIMZAI, M., MUGABE, F., GEORGE, U., CALNAN, J. & SEYOUM, D. 2018. Improving TB case notification in northern Uganda: evidence of a quality improvement-guided active case finding intervention. *BMC health services research,* 18**,** 1-12.

KARIM, F., ISLAM, M. A., CHOWDHURY, A., JOHANSSON, E. & DIWAN, V. K. 2007. Gender differences in delays in diagnosis and treatment of tuberculosis. *Health policy and planning,* 22**,** 329-334.

KEMP, J. R., MANN, G., SIMWAKA, B. N., SALANIPONI, F. M. & SQUIRE, S. B. 2007. Can Malawi's poor afford free tuberculosis services? Patient and household costs associated with a tuberculosis diagnosis in Lilongwe. *Bulletin of the World Health Organization,* 85**,** 580-585.

KENDALL, E. A., SAHU, S., PAI, M., FOX, G. J., VARAINE, F., COX, H., CEGIELSKI, J. P., MABOTE, L., VASSALL, A. & DOWDY, D. W. 2019. What will it take to eliminate drug-resistant tuberculosis? *The International Journal of Tuberculosis and Lung Disease,* 23**,** 535-546.

KHANAL, S., ELSEY, H., KING, R., BARAL, S. C., BHATTA, B. R. & NEWELL, J. N. 2017. Development of a patient-centred, psychosocial support intervention for multi-drug-resistant tuberculosis (MDR-TB) care in Nepal. *PloS one,* 12.

KHILNANI, G. 2004. Tuberculosis and pregnancy. *Indian Journal of Chest Diseases and Allied Sciences,* 46**,** 105-112.

KNOBLAUCH, A. M., LAPIERRE, S. G., RANDRIAMANANA, D., RAHERISON, M. S., RAKOTOSON, A., RAHOLIJAONA, B. S., RAVAOARIMANGA, M., RAVOLOLONANDRIANA, P. E., RABODOARIVELO, M.-S. & RATSIRAHONANA, O. 2020. Multidrug-resistant tuberculosis surveillance and cascade of care in Madagascar: a five-year (2012–2017) retrospective study. *BMC medicine,* 18**,** 1-14.

KOEHN, P. H. 2018. *Transnational mobility and global health: Traversing borders and boundaries*, Routledge.

KOPLAN, J. P., BOND, T. C., MERSON, M. H., REDDY, K. S., RODRIGUEZ, M. H., SEWANKAMBO, N. K. & WASSERHEIT, J. N. 2009. Towards a common definition of global health. *The Lancet,* 373**,** 1993-1995.

KREFTING, L. 1991. Rigor in qualitative research: The assessment of trustworthiness. *American journal of occupational therapy,* 45**,** 214-222.

KRUK, M. E. & FREEDMAN, L. P. 2008. Assessing health system performance in developing countries: a review of the literature. *Health policy,* 85**,** 263-276.

KRUK, M. E., LARSON, E. & TWUM-DANSO, N. A. 2016. Time for a quality revolution in global health. *Lancet Glob Health,* 4**,** e594-6.

KURA, S. M. & YERO, B. U. 2013. An analysis of gender inequality and national gender policy in Nigeria. *International Journal of Scientific & Engineering Research,* 4**,** 1-23.

KWEZA, P. F., VAN SCHALKWYK, C., ABRAHAM, N., UYS, M., CLAASSENS, M. M. & MEDINA-MARINO, A. 2018. Estimating the magnitude of pulmonary tuberculosis patients missed by primary health care clinics in South Africa. *International Journal of Tuberculosis and Lung Disease,* 22**,** 264-+.

LALONDE, M. 1974. *A new perspective on the health of Canadians: a working document*, Ottawa.

LAURENCE, Y. V., GRIFFITHS, U. K. & VASSALL, A. 2015. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. *PharmacoEconomics,* 33**,** 939-955.

LAW, S., DAFTARY, A., O'DONNELL, M., PADAYATCHI, N., CALZAVARA, L. & MENZIES, D. 2019. Interventions to improve retention-in-care and treatment adherence among patients with drug-resistant tuberculosis: a systematic review. *European Respiratory Journal,* 53.

LEACH, M. 2020. Echoes of Ebola: social and political warnings for the COVID-19 response in African settings. *Echoes*.

LEVESQUE, J.-F., HARRIS, M. F. & RUSSELL, G. 2013. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *International journal for equity in health,* 12**,** 1.

LEVY, B. S. & SIDEL, V. W. 2013. *Social injustice and public health*, Oxford University Press.

LIU, Y., BI, L., CHEN, Y., WANG, Y., FLEMING, J., YU, Y., GU, Y., LIU, C., FAN, L. & WANG, X. 2020a. Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. *medRxiv*.

LIU, Y., GAYLE, A. A., WILDER-SMITH, A. & ROCKLÖV, J. 2020b. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *Journal of travel medicine*.

LOVEDAY, M., THOMSON, L., CHOPRA, M. & NDLELA, Z. 2008. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. *International Journal of Tuberculosis and Lung Disease,* 12**,** 1042-1047.

MA, Y., HORSBURGH, C., WHITE, L. F. & JENKINS, H. E. 2018. Quantifying TB transmission: a systematic review of reproduction number and serial interval estimates for tuberculosis. *Epidemiology & Infection,* 146**,** 1478-1494.

MACINTYRE, K., BAKKER, M. I., BERGSON, S., BHAVARAJU, R., BOND, V., CHIKOVORE, J., COLVIN, C., CRAIG, G., CREMERS, A. & DAFTARY, A. 2017. Defining the research agenda to measure and reduce tuberculosis stigmas. *The international journal of tuberculosis and lung disease,* 21**,** S87-S96.

MAFFIOLI, E. M. 2020. How Is the World Responding to the Novel Coronavirus Disease (COVID-19) Compared with the 2014 West African Ebola Epidemic? The Importance of China as a Player in the Global Economy. *The American Journal of Tropical Medicine and Hygiene,* 102**,** 924-925.

MAKINDE, O. A., SULE, A., AYANKOGBE, O. & BOONE, D. 2018. Distribution of health facilities in Nigeria: implications and options for universal health coverage. *The International journal of health planning and management,* 33**,** e1179-e1192.

MANYAZEWAL, T. 2017. Using the World Health Organization health system building blocks through survey of healthcare professionals to determine the performance of public healthcare facilities. *Archives of Public Health,* 75**,** 50.

MARMOT, M., ALLEN, J., BELL, R., BLOOMER, E. & GOLDBLATT, P. 2012. WHO European review of social determinants of health and the health divide. *The lancet,* 380**,** 1011-1029.

MARMOT, M., FRIEL, S., BELL, R., HOUWELING, T. A., TAYLOR, S. & HEALTH, C. O. S. D. O. 2008. Closing the gap in a generation: health equity through action on the social determinants of health. *The Lancet,* 372**,** 1661-1669.

MATHAD, J. S. & GUPTA, A. 2012. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clinical infectious diseases,* 55**,** 1532-1549.

MATTEELLI, A., SULIS, G., CAPONE, S., D'AMBROSIO, L., MIGLIORI, G. B. & GETAHUN, H. 2017. Tuberculosis elimination and the challenge of latent tuberculosis. *La Presse Médicale,* 46**,** e13-e21.

MAUCH, V., BONSU, F., GYAPONG, M. & AWINI…, E. 2013. Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents.

MCKENNA, N. 1992. A dangerous liaison: tuberculosis and HIV. *WorldAIDS***,** 3 p.

MCLAREN, Z. M., SHARP, A. R., ZHOU, J., WASSERMAN, S. & NANOO, A. 2017. Assessing healthcare quality using routine data: evaluating the performance of the national tuberculosis programme in South Africa. *Tropical Medicine and International Health,* 22**,** 171-179.

MCLEROY, K. R., BIBEAU, D., STECKLER, A. & GLANZ, K. 1988. An ecological perspective on health promotion programs. *Health education quarterly,* 15**,** 351-377.

MCQUAID, C. F., MCCREESH, N., READ, J. M., SUMNER, T., HOUBEN, R. M., WHITE, R. G. & HARRIS, R. C. 2020. The potential impact of COVID-19-related disruption on tuberculosis burden. *European Respiratory Journal*.

MEIRING, C., VAN HELDEN, P. D. & GOOSEN, W. J. 2018. TB control in humans and animals in South Africa: a perspective on problems and successes. *Frontiers in veterinary science,* 5**,** 298.

MERESSA, D., HURTADO, R. M., ANDREWS, J. R., DIRO, E., ABATO, K., DANIEL, T., PRASAD, P., PRASAD, R., FEKADE, B. & TEDLA, Y. 2015. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax,* 70**,** 1181-1188.

MERTENS, D. M. 2007. Transformative paradigm: Mixed methods and social justice. *Journal of mixed methods research,* 1**,** 212-225.

METCALFE, J. Z., MAKUMBIROFA, S., MAKAMURE, B., SANDY, C., BARA, W., MASON, P. & HOPEWELL, P. C. 2016. Xpert® MTB/RIF detection of rifampin resistance and time to treatment initiation in Harare, Zimbabwe. *The International Journal of Tuberculosis and Lung Disease,* 20**,** 882-889.

MILES, M. B. & HUBERMAN, A. M. 1994. Qualitative data analysis: A sourcebook. *Beverly Hills: Sage Publications*.

MNYAMBWA, N. P., LEKULE, I., NGADAYA, E. S., KIMARO, G., PETRUCKA, P., KIM, D.-J., LYMO, J., KAZWALA, R., MOSHA, F. & MFINANGA, S. G. 2018. Assessment of GeneXpert GxAlert platform for multi-drug resistant tuberculosis diagnosis and patients' linkage to care in Tanzania. *BMC research notes,* 11**,** 121.

MOHER, D., LIBERATI, A., TETZLAFF, J. & ALTMAN, D. G. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine,* 151**,** 264-269.

MOHR, E., DANIELS, J., MULLER, O., FURIN, J., CHABALALA, B., STEELE, S., COX, V., DOLBY, T., FERLAZZO, G. & SHROUFI, A. 2017. Missed opportunities for earlier diagnosis of rifampicin-resistant tuberculosis despite access to Xpert® MTB/RIF. *The International Journal of Tuberculosis and Lung Disease,* 21**,** 1100-1105.

MOSER, A. & KORSTJENS, I. 2018. Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. *European Journal of General Practice,* 24**,** 9-18.

MOUNIER-JACK, S., GRIFFITHS, U. K., CLOSSER, S., BURCHETT, H. & MARCHAL, B. 2014. Measuring the health systems impact of disease control programmes: a critical reflection on the WHO building blocks framework. *BMC public health,* 14**,** 278.

MOYO, S., FURIN, J. J., HUGHES, J., DANIELS, J., SNYMAN, L., MULLER, O., COX, V., SHROUFI, A. & COX, H. 2014. Outcomes in adolescents undergoing treatment for drug-resistant tuberculosis in Cape Town, South Africa, 2008-2013. *Archives of Pediatric Infectious Diseases*.

MPAGAMA, S. G., HEYSELL, S. K., NDUSILO, N. D., KUMBURU, H. H., LEKULE, I. A., KISONGA, R. M., GRATZ, J., BOEREE, M. J., HOUPT, E. R. & KIBIKI, G. S. 2013. Diagnosis and interim treatment outcomes from the first cohort of multidrug-resistant tuberculosis patients in Tanzania. *PLoS One,* 8**,** e62034.

MUNRO, S. A., LEWIN, S. A., SMITH, H. J., ENGEL, M. E. & FRETHEIM…, A. 2007. Patient adherence to tuberculosis treatment: a systematic review of qualitative research.

MURPHY, E., DINGWALL, R., GREATBATCH, D., PARKER, S. & WATSON, P. 1998. Qualitative research methods in health technology assessment: a review of the literature.

MUSGROVE, P. 1986. Measurement of equity in health. *World health statistics quarterly 1986; 39 (4): 325-335*.

MUSTAPHA, G., JUMOKE, O., NWADIKE, P., EMEKA, E., AKANG, G., ENEOGU, R., CHUKWUEME, N., ALIYU, G. & BHATTA, G. 2015. Assessment of Gene-xpert MTB RIF program implementation and the challenges for enhanced tuberculosis diagnosis in Nigeria. *SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS,* 12**,** 1-7.

NAIDOO, A., NAIDOO, S., GATHIRAM, P. & LALLOO, U. 2013. Tuberculosis in medical doctors - a study of personal experiences and attitudes. *Samj South African Medical Journal,* 103**,** 176-180.

NAIDOO, P., DU TOIT, E., DUNBAR, R., LOMBARD, C., CALDWELL, J., DETJEN, A., SQUIRE, S. B., ENARSON, D. A. & BEYERS, N. 2014a. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS ONE,* 9.

NAIDOO, P., DU TOIT, E., DUNBAR, R., LOMBARD, C., CALDWELL, J., DETJEN, A., SQUIRE, S. B., ENARSON, D. A. & BEYERS, N. 2014b. A comparison of multidrug-resistant tuberculosis treatment commencement times in MDRTBPlus line probe assay and Xpert® MTB/RIF-based algorithms in a routine operational setting in Cape Town. *PLoS One,* 9**,** e103328.

NAIDOO, P., THERON, G., RANGAKA, M. X., CHIHOTA, V. N., VAUGHAN, L., BREY, Z. O. & PILLAY, Y. 2017. The South African tuberculosis care cascade: estimated losses and methodological challenges. *The Journal of infectious diseases,* 216**,** S702-S713.

NAIDOO, P., VAN NIEKERK, M., DU TOIT, E., BEYERS, N. & LEON, N. 2015a. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests. *BMC health services research,* 15**,** 488.

NAIDOO, P., VAN NIEKERK, M., DU TOIT, E., BEYERS, N. & LEON, N. 2015b. Pathways to multidrug-resistant tuberculosis diagnosis and treatment initiation: a qualitative comparison of patients' experiences in the era of rapid molecular diagnostic tests. *Bmc Health Services Research,* 15.

NATIONAL BUREAU OF STATISTICS 2016. DEMOGRAPHIC STATISTICS BULLETIN 2015. Abuja, Nigeria: National Bureau of Statistics Nigeria.

NATIONAL BUREAU OF STATISTICS 2017. DEMOGRAPHIC STATISTICS BULLETIN 2016. Abuja, Nigeria: National Bureau of Statistics Nigeria.

NBLCP/FMOH 2015a. e-TB Manager Treatment Database. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH 2015b. GxAlert Gene Xpert Database. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NBLCP/FMOH. 2015. 2015 Annual Report, National Tuberculosis and Leprosy Control Programme. . Nigeria:.

NBLCP/FMOH. 2019. 2019 Annual TB Report. *In:* PROGRAMME., N. T. A. L. C. (ed.). Nigeria:.

NBS 2016a. DEMOGRAPHIC STATISTICS BULLETIN 2015. . *In:* NATIONAL BUREAU OF STATISTICS NIGERIA, D. D. N. (ed.). Abuja, Nigeria: .

NBS 2016b. National Population Estimates 2006-2016. Abuja, Nigeria: National Bureau of Statistics Nigeria.

NBS 2017. DEMOGRAPHIC STATISTICS BULLETIN 2017. Abuja, Nigeria: National Bureau of Statistics Nigeria.

NGAMVITHAYAPONG-YANAI, J. 2016. The role of qualitative research in ending TB. *Public Health Action,* 6**,** 209.

NICOLA, M., ALSAFI, Z., SOHRABI, C., KERWAN, A., AL-JABIR, A., IOSIFIDIS, C., AGHA, M. & AGHA, R. 2020. The socio-economic implications of the coronavirus and COVID-19 pandemic: a review. *International Journal of Surgery*.

NISHIURA, H., LINTON, N. M. & AKHMETZHANOV, A. R. 2020. Serial interval of novel coronavirus (COVID-19) infections. *International journal of infectious diseases*.

NKOSI, D., JANSSEN, S., PADANILAM, X., LOUW, R., MENEZES, C. N. & GROBUSCH, M. P. 2013. Factors influencing specialist care referral of multidrug- and extensively drug-resistant tuberculosis patients in Gauteng/South Africa: a descriptive questionnaire-based study. *BMC Health Services Research,* 13.

NNAMANI, N. & MEJEHA, R. EFFECT OF LENDING CRITERIA ON FEMALES'ACCESS TO CREDIT FROM BANK OF AGRICULTURE ABIA STATE, NIGERIA.

NTBLCP, F. 2008. THE NATIONAL GUIDELINES FOR TB INFECTION CONTROL. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NTBLCP, F. 2010. Workers' Manual. *In:* FEDERAL MINISTRY OF HEALTH, N. (ed.).

NTBLCP, F. 2012. First National TB Prevalence Survey Nigeria. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NTBLCP, F. 2014. The National Strategic Plan for Tuberculosis Control: Towards Universal Access to Prevention, Diagnosis and Treatment- 2015-2020. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NTBLCP, F. 2015a. 2015 Annual Report National Tuberculosis and Leprosy Control Programme. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NTBLCP, F. 2015b. DR-TB Program Data. Nigeria: National Tuberculosis & Leprosy Control Program, Federal Ministry of Health

NTBLCP, F. 2017a. Guidelines on the Use of the Shorter Regimen and New Drugs in the Clinical and Programmatic Management of Drug Resistant Tuberculosis and Co-Infections of Nigeria *In:* FEDERAL MINISTRY OF HEALTH, N. (ed.).

NTBLCP, F. 2017b. NTBLCP Xpert machines as at the end of Q3, 2017.

O'HARA, N. N., ROY, L., O'HARA, L. M., SPIEGEL, J. M., LYND, L. D., FITZGERALD, J. M., YASSI, A., NOPHALE, L. E. & MARRA, C. A. 2015. Healthcare Worker Preferences for Active Tuberculosis Case Finding Programs in South Africa: A Best-Worst Scaling Choice Experiment. *Plos One,* 10.

OBINNA UDODIRI, N., JAVED GHULAM, H., HATEM, E.-G., EDWARDS, D. & ERNEST, O. 2019. Dynamics of Group Lending Mechanism and the Role of Group Leaders in Developing

Countries: Evidence from Nigeria. *International Journal of Customer Relationship Marketing and Management*.

OECD. 2020. *The territorial impact of COVID-19: Managing the crisis across levels of government* [Online]. Available: https://read.oecd-ilibrary.org/view/?ref=128_128287-5agkkojaaa&title=The-territorial-impact-of-covid-19-managing-the-crisis-across-levels-of-government [Accessed].

OGA-OMENKA, C., BADA, F., AGBAJE, A., DAKUM, P., MENZIES, D. & ZAROWSKY, C. 2020a. Ease and equity of access to free DR-TB services in Nigeria-a qualitative analysis of policies, structures and processes.

OGA-OMENKA, C., BOFFA, J., KUYE, J., DAKUM, P., MENZIES, D. & ZAROWSKY, C. 2020b. Understanding the Gaps in DR-TB Care Cascade in Nigeria: a sequential mixed-method study. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 100193.

OGA-OMENKA C, J. M., ZAROWSKY C, 2016. The evidence regarding health system barriers and facilitators to multi-drug resistant tuberculosis case detection in Africa- A Scoping Review. Montreal, Canada: Université de montreal.

OGA-OMENKA, C., TSEJA-AKINRIN, A., SEN, P., MAC-SEING, M., AGBAJE, A., MENZIES, D. & ZAROWSKY, C. 2020c. Factors influencing diagnosis and treatment initiation for multidrug-resistant/rifampicin-resistant tuberculosis in six sub-Saharan African countries: a mixed-methods systematic review. *BMJ Global Health,* 5**,** e002280.

OGA-OMENKA, C., ZAROWSKY, C., AGBAJE, A., KUYE, J. & MENZIES, D. 2019. Rates and timeliness of treatment initiation among drug-resistant tuberculosis patients in Nigeria-A retrospective cohort study. *PloS one,* 14.

OGBUABOR, D. C. 2020. Through service providers' eyes: health systems factors affecting implementation of tuberculosis control in Enugu State, South-Eastern Nigeria. *BMC Infect Dis,* 20**,** 206.

OKEIBUNOR, J. C., ONYENEHO, N. G., CHUKWU, J. N. & POST, E. 2006. Barriers to care seeking in directly observed therapy short-course (DOTS) clinics and tuberculosis control in southern Nigeria: a qualitative analysis. *International quarterly of community health education,* 27**,** 23-37.

OKEIBUNOR, J. C., ONYENEHO, N. G., CHUKWU, J. N. & POST, E. 2007. Barriers to care seeking in directly observed therapy short-course (DOTS) clinics and tuberculosis control in southern Nigeria: a qualitative analysis. *International quarterly of community health education,* 27**,** 23-37.

OKOT-CHONO, R., MUGISHA, F., ADATU, F., MADRAA, E., DLODLO, R. & FUJIWARA, P. 2009. Health system barriers affecting the implementation of collaborative TB-HIV services in Uganda. *The international journal of tuberculosis and lung disease,* 13**,** 955-961.

OLIVER, A. & MOSSIALOS, E. 2004. Equity of access to health care: outlining the foundations for action. *Journal of Epidemiology & Community Health,* 58**,** 655-658.

OLIWA, J., MAINA, J., AYIEKO, P., GATHARA, D., KATHURE, I., MASINI, E., VAN'T HOOG, A., VAN HENSBROEK, M. & ENGLISH, M. 2018. Variability in distribution and use of tuberculosis diagnostic tests in Kenya: a cross-sectional survey. *BMC infectious diseases,* 18**,** 328.

OLUKOLADE, R., HASSAN, A., OGBUJI, Q., OLUJIMI, S., OKWUONYE, L., KUSIMO, O., OKECHUKWU, J., OSHO, J., OSINOWO, K. & LADIPO, O. 2017. Role of treatment supporters beyond monitoring daily drug intake for TB-patients: findings from a qualitative study in Nigeria. *Journal of Public Health and Epidemiology,* 9**,** 65-73.

OLUWABAMIDE, A. J. & UMOH, J. O. 2011. An assessment of the relevance of religion to health care delivery in Nigeria: case of Akwa Ibom State. *Journal of Sociology and Social Anthropology,* 2**,** 47-52.

OMENKA, C. O. 2010. *Factors influencing access to antiretroviral treatment in Benue State, Nigeria.* University of the Western Cape.

ONAZI, O., GIDADO, M., ONAZI, M. & DANIEL…, O. 2015. Estimating the cost of TB and its social impact on TB patients and their households.

ONIFADE, D. A., BAYER, A. M., MONTOYA, R., HARO, M., ALVA, J., FRANCO, J., SOSA, R., VALIENTE, B., VALERA, E. & FORD, C. M. 2010. Gender-related factors influencing tuberculosis control in shantytowns: a qualitative study. *BMC Public Health,* 10**,** 381.

ONYEDUM, C. C., ALOBU, I. & UKWAJA, K. N. 2017. Prevalence of drug-resistant tuberculosis in Nigeria: A systematic review and meta-analysis. *PloS one,* 12.

ONYENEHO, N. G. & CHUKWU, J. N. 2010. Is there a role for patent medicine vendors in tuberculosis control in southern Nigeria? *Journal of health, population, and nutrition,* 28**,** 567.

ORGANIZATION, W. H. 2015. Gear up to end TB: introducing the end TB strategy. World Health Organization.

ORGANIZATION, W. H. 2018. Engaging private health care providers in TB care and prevention: a landscape analysis. World Health Organization.

ORGANIZATION, W. H. 2020. Global health observatory (GHO) data. 2020.

ORTBLAD, K. F., SALOMON, J. A., BÄRNIGHAUSEN, T. & ATUN, R. 2015. Stopping tuberculosis: a biosocial model for sustainable development. *The Lancet,* 386**,** 2354-2362.

OSBORN, D., CUTTER, A. & ULLAH, F. Universal sustainable development goals. Understanding the transformational Challenge for Developed Countries. Report of Study by Stakeholder Forum, 2015.

OSHI, D., CHUKWU, J., NWAFOR, C., CHUKWU, N. E., MEKA, A. O., ANYIM, M., UKWAJA, K. N., ALOBU, I., EKEKE, N. & OSHI, S. N. 2019. Support and unmet needs of patients undergoing multidrug-resistant tuberculosis (MDR-TB) treatment in southern Nigeria. *Int J Health Plann Manage*.

OSHI, D., CHUKWU, J., NWAFOR, C., CHUKWU, N. E., MEKA, A. O., ANYIM, M., UKWAJA, K. N., ALOBU, I., EKEKE, N. & OSHI, S. N. 2020. Support and unmet needs of patients undergoing multidrug-resistant tuberculosis (MDR-TB) treatment in southern Nigeria. *The International journal of health planning and management,* 35**,** 832-842.

OSHI, D. C. 2009. *Rural women and the financing of health care in Nigeria.* Institute of Social Studies.

OSHI, D. C., OSHI, S. N., ALOBU, I. N. & UKWAJA, K. N. 2016a. Gender-related factors influencing women's health seeking for tuberculosis care in Ebonyi state, Nigeria. *Journal of biosocial science,* 48**,** 37-50.

OSHI, D. C., OSHI, S. N., ALOBU, I. N. & UKWAJA, K. N. 2016b. Gender-related factors influencing women’s health seeking for tuberculosis care in Ebonyi State, Nigeria. *J Biosoc Sci,* 48**,** 37-50.

OTU, A. A. 2013. A review of the national tuberculosis and leprosy control programme (ntblcp) of Nigeria: challenges and prospects. *Annals of Tropical Medicine and Public Health,* 6**,** 491.

OYEBOLA, D. 1980. Traditional medicine and its practitioners among the Yoruba of Nigeria: a classification. *Social Science & Medicine. Part A: Medical Psychology & Medical Sociology,* 14**,** 23-29.

PABLOS-MÉNDEZ, A., STERLING, T. R. & FRIEDEN, T. R. 1996. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. *Jama,* 276**,** 1223-1228.

PACE, R., PLUYE, P., BARTLETT, G., MACAULAY, A. C., SALSBERG, J., JAGOSH, J. & SELLER, R. 2012. Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. *International journal of nursing studies,* 49**,** 47-53.

PAI, M. 2019. Drug-Resistant TB: A Clear And Present Danger. *Forbes.*

PAI, M. 2020a. AIDS, TB And Malaria: Coronavirus Threatens The Endgame. *Forbes*, 29 March 2020.

PAI, M. 2020b. COVID-19 Coronavirus And Tuberculosis: We Need A Damage Control Plan. *Forbes*, 17 March 2020.

PAI, M. & MEMISH, Z. A. 2019. Antimicrobial resistance and the growing threat of drug-resistant tuberculosis. *Journal of epidemiology and global health,* 6**,** 45-47.

PAI, M. & TEMESGEN, Z. 2019. Quality: the missing ingredient in TB care and control. *Journal of clinical tuberculosis and other mycobacterial diseases,* 14**,** 12.

PANG, Y., LIU, Y., DU, J., GAO, J. & LI, L. Impact of COVID-19 on tuberculosis control in China.

PARRISH, N. M., DICK, J. D. & BISHAI, W. R. 1998. Mechanisms of latency in Mycobacterium tuberculosis. *Trends in microbiology,* 6**,** 107-112.

PENCHANSKY, R. & THOMAS, J. W. 1981. The concept of access: definition and relationship to consumer satisfaction. *Medical care***,** 127-140.

PERCIVAL, V., RICHARDS, E., MACLEAN, T. & THEOBALD, S. 2014. Health systems and gender in post-conflict contexts: building back better? *Conflict and Health,* 8**,** 19.

PHARMACCESS 2016. A Closer Look at the Healthcare System in Nigeria. *In:* PHARMACCESS (ed.).

PIOTROW, P. T. & DE FOSSARD, E. 2003. Entertainment-education as a public health intervention. *Entertainment-education and social change.* Routledge.

PIRTLE, W. N. L. 2020. Racial capitalism: a fundamental cause of novel coronavirus (COVID-19) pandemic inequities in the United States. *Health Education & Behavior*.

POPE, C. & MAYS, N. 1995. Qualitative research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *Bmj,* 311**,** 42-45.

PRICE, A. J., CRAMPIN, A. C., AMBERBIR, A., KAYUNI-CHIHANA, N., MUSICHA, C., TAFATATHA, T., BRANSON, K., LAWLOR, D. A., MWAIYEGHELE, E. & NKHWAZI, L. 2018. Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi. *The lancet Diabetes & endocrinology,* 6**,** 208-222.

PRITCHETT, L. 2006. Who is not poor? Dreaming of a world truly free of poverty. *The World Bank Research Observer,* 21**,** 1-23.

PRÜSS-ÜSTÜN, A. 2016. *Preventing disease through healthy environments: A global assessment of the burden of disease from environmental risks*.

RAINE, R., OR, Z., PRADY, S. & BEVAN, G. 2016. Evaluating health-care equity. *Challenges, solutions and future directions in the evaluation of service innovations in health care and public health.* NIHR Journals Library.

RAISI-ESTABRAGH, Z., MCCRACKEN, C., BETHELL, M. S., COOPER, J., COOPER, C., CAULFIELD, M. J., MUNROE, P. B., HARVEY, N. C. & PETERSEN, S. E. 2020. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25 (OH)-vitamin D status: study of 1326 cases from the UK Biobank. *Journal of Public Health*.

RAMMA, L., COX, H., WILKINSON, L., FOSTER, N., CUNNAMA, L., VASSALL, A. & SINANOVIC, E. 2015. Patients' costs associated with seeking and accessing treatment for drug-resistant tuberculosis in South Africa. *International Journal of Tuberculosis & Lung Disease,* 19**,** 1513-9.

RANGAKA, M. X., CAVALCANTE, S. C., MARAIS, B. J., THIM, S., MARTINSON, N. A., SWAMINATHAN, S. & CHAISSON, R. E. 2015. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *The Lancet,* 386**,** 2344-2353.

RASANATHAN, K., SIVASANKARA KURUP, A., JARAMILLO, E. & LÖNNROTH, K. 2011. The social determinants of health: key to global tuberculosis control. *The International Journal of Tuberculosis and Lung Disease,* 15**,** S30-S36.

REEVE, E., TO, J., HENDRIX, I., SHAKIB, S., ROBERTS, M. S. & WIESE, M. D. 2013. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs & aging,* 30**,** 793-807.

RIDGEWAY, C. L. 2009. Framed before we know it: How gender shapes social relations. *Gender & society,* 23**,** 145-160.

RILEY, R. 1957. Aerial dissemination of pulmonary tuberculosis. *American Review of Tuberculosis and pulmonary Diseases,* 76**,** 931-41.

RILEY, R., MILLS, C., NYKA, W., WEINSTOCK, N., STOREY, P., SULTAN, L., RILEY, M. & WELLS, W. 1959. Aerial dissemination of pulmonary tuberculosis. A two-year study of contagion in a tuberculosis ward. *American Journal of Hygiene,* 70**,** 185-96.

RING, N. A., RITCHIE, K., MANDAVA, L. & JEPSON, R. 2011. A guide to synthesising qualitative research for researchers undertaking health technology assessments and systematic reviews.

ROOD, E., MERGENTHALER, C., BAKKER, M., REDWOOD, L. & MITCHELL, E. 2017. Using 15 DHS surveys to study epidemiological correlates of TB courtesy stigma and health-seeking behaviour. *The International Journal of Tuberculosis and Lung Disease,* 21**,** S60-S68.

ROSCOE, C., NAMIBIA, C., KALAPILA, A. G., SPACH, D. H. & AETC, M. W. 2020. *Retention in HIV care* [Online]. Available: https://www.hiv.uw.edu/go/basic-primary-care/retention-care/core-concept/all [Accessed].

RUBENSTEIN, L., HEMPEL, S., DANZ, M., ROSE, D., STOCKDALE, S., CURTIS, I. & KIRSH, S. 2020. Eight Priorities for Improving Primary Care Access Management in Healthcare Organizations: Results of a Modified Delphi Stakeholder Panel. *Journal of general internal medicine,* 35**,** 523-530.

SAHN, D. E. & STIFEL, D. C. 2003. Urban–rural inequality in living standards in Africa. *Journal of African Economies,* 12**,** 564-597.

SALTER, K., HELLINGS, C., FOLEY, N. & TEASELL, R. 2008. The experience of living with stroke: a qualitative meta-synthesis. *Journal of rehabilitation medicine,* 40**,** 595-602.

SANDS, P. 2020a. HIV, tuberculosis, and malaria: how can the impact of COVID-19 be minimised? *The Lancet. Global Health*.

SANDS, P. 27 March 2020 2020b. Re-thinking Global Health Security. *Voices: News and Stories* [Online]. Available from: https://www.theglobalfund.org/en/blog/2020-03-27-re-thinking-global-health-security/.

SAPPENFIELD, E., JAMIESON, D. J. & KOURTIS, A. P. 2013. Pregnancy and susceptibility to infectious diseases. *Infectious diseases in obstetrics and gynecology,* 2013.

SARGENT, C. & LARCHANCHÉ, S. 2011. Transnational migration and global health: the production and management of risk, illness, and access to care. *Annual Review of Anthropology,* 40**,** 345-361.

SCHAAF, H., SHEAN, K. & DONALD, P. 2003. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Archives of disease in childhood,* 88**,** 1106-1111.

SCOTT, N., DOYLE, J. S., WILSON, D. P., WADE, A., HOWELL, J., PEDRANA, A., THOMPSON, A. & HELLARD, M. E. 2017. Reaching hepatitis C virus elimination targets requires health system interventions to enhance the care cascade. *International Journal of Drug Policy,* 47**,** 107-116.

SEALE, C. 1999. Chap 4: Guiding ideals. *Quality in qualitative research.* Thousand Oaks: Sage Publications.

SEN, A. 2002. Why health equity? *Health Econ,* 11**,** 659-66.

SHADMI, E., CHEN, Y., DOURADO, I., FARAN-PERACH, I., FURLER, J., HANGOMA, P., HANVORAVONGCHAI, P., OBANDO, C., PETROSYAN, V. & RAO, K. D. 2020. Health equity and COVID-19: global perspectives. *International journal for equity in health,* 19**,** 1-16.

SHARMA, N., TANEJA, D., PAGARE, D., SAHA, R., VASHIST, R. & INGLE, G. 2005. The impact of an IEC campaign on tuberculosis awareness and health seeking behaviour in Delhi, India. *The International Journal of Tuberculosis and Lung Disease,* 9**,** 1259-1265.

SHARMA, R., YADAV, R., SHARMA, M., SAINI, V. & KOUSHAL, V. 2014. Quality of life of multi drug resistant tuberculosis patients: a study of north India. *Acta Medica Iranica***,** 448-453.

SHARMA, S. K. & MOHAN, A. 2006. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. *Chest,* 130**,** 261-272.

SHENGELIA, B., MURRAY, C. J. & ADAMS, O. B. 2003. Beyond access and utilization: defining and measuring health system coverage. *Health systems performance assessment: debates, methods and empiricism. Geneva: World Health Organization***,** 221-34.

SIMPSON, J. 2009. *Everyone belongs: A toolkit for applying intersectionality*, Canadian Research Institute for the Advancement of Women (CRIAW) Ottawa.

STALIN, P., MANIKANDAN, M., ANTONY, V., MURUGAN, N., SINGH, Z., KISKU, K. H., PURTY, A. J., VASUDEVAN, K., CHERIAN, J. & BABU, V. 2020. Identifying and addressing factors contributing to pretreatment loss to follow-up of tuberculosis patients referred for treatment from medical colleges in Pondicherry: An implementation research. *Indian Journal of Community Medicine,* 45**,** 27.

STOP TB INDONESIA 2020. Challenges & Recommendations of TB Program during the COVID-19 pandemic.

STOPTB Partnership. 2020."The Potential Impact of the Covid-19 Response on Tuberculosis in High-Burden Countries: Modelling Analysis.".
STOPTB PARTNERSHIP. 2020. *We did a rapid assessment: The TB Response is Heavily Impacted by the COVID-19 Pandemic* [Online]. Available: http://www.stoptb.org/news/stories/2020/ns20_014.html. [Accessed 08 April 2020].
STORLA, D. G., YIMER, S. & BJUNE, G. A. 2008. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC public health,* 8**,** 1.
STROBE STATEMENT. 2007. *STROBE Statement - Checklist of items that shouldbe included in reports of observational studies* [Online]. Available: https://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf [Accessed 15 September 2018].
SUBBARAMAN, R., NATHAVITHARANA, R. R., MAYER, K. H., SATYANARAYANA, S., CHADHA, V. K., ARINAMINPATHY, N. & PAI, M. 2019a. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLoS medicine,* 16**,** e1002754.
SUBBARAMAN, R., NATHAVITHARANA, R. R., MAYER, K. H., SATYANARAYANA, S., CHADHA, V. K., ARINAMINPATHY, N. & PAI, M. 2019b. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. *PLoS medicine,* 16.
SUBBARAMAN, R., NATHAVITHARANA, R. R., SATYANARAYANA, S., PAI, M., THOMAS, B. E., CHADHA, V. K., RADE, K., SWAMINATHAN, S. & MAYER, K. H. 2016. The tuberculosis cascade of care in India's public sector: a systematic review and meta-analysis. *PLoS medicine,* 13**,** e1002149.
SULLIVAN, B. J., ESMAILI, B. E. & CUNNINGHAM, C. K. 2017. Barriers to initiating tuberculosis treatment in sub-Saharan Africa: a systematic review focused on children and youth. *Global health action,* 10**,** 1290317.
SWEETMAN, D., BADIEE, M. & CRESWELL, J. W. 2010. Use of the transformative framework in mixed methods studies. *Qualitative inquiry,* 16**,** 441-454.
TANIMURA, T., JARAMILLO, E. & WEIL..., D. 2014. Financial burden for tuberculosis patients in low-and middle-income countries: a systematic review.
TARIMO, G. B. 2012. *Delay in seeking care among tuberculosis patients attending tuberculosis clinics in Rungwe district, Tanzania.* Muhimbili University of Health and Allied Sciences.
TB CIVIL SOCIETY ORGANIZATIONS 2020. The impact of COVID-19 on the TB epidemic: A community perspective.
TB DOTS STRATEGY COORDINATION 2014. National Tuberculosis Management Guidelines. *In:* HEALTH, N. D. O. (ed.). Republic of South Africa: Dept of Health, RSA.
TEDDLIE, C. & TASHAKKORI, A. 2009. *Foundations of mixed methods research: Integrating quantitative and qualitative approaches in the social and behavioral sciences*, Sage.
TESHOME, D. 2010. *Non-performing Loan and Its Management in Ethiopia: A case study on Dashen Bank Mekelle Area Bank, in Tigray.* Mekelle University.
THE WORLD BANK. 2015. *"World Bank Forecasts Global Poverty to Fall Below 10% for First Time; Major Hurdles Remain in Goal to End Poverty by 2030". Retrieved 6 October 2015.* [Online]. Washington: The World Bank. Available: http://www.worldbank.org/en/news/press-release/2015/10/04/world-bank-forecasts-

global-poverty-to-fall-below-10-for-first-time-major-hurdles-remain-in-goal-to-end-poverty-by-2030 [Accessed October 25th 2016].

THE WORLD BANK. 2016. *Current health expenditure (% of GDP) - Sub-Saharan Africa* [Online]. Available: https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?contextual=max&locations=ZG-1W [Accessed 05 May 2020 2020].

THOMAS, B. E., SHANMUGAM, P., MALAISAMY, M., OVUNG, S., SURESH, C., SUBBARAMAN, R., ADINARAYANAN, S. & NAGARAJAN, K. 2016. Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review. *Plos One,* 11**,** 15.

THOMAS, B. E., SURESH, C., LAVANYA, J., LINDSLEY, M. M., GALIVANCHE, A. T., SELLAPPAN, S., OVUNG, S., ARAVIND, A., LINCY, S. & RAJA, A. L. 2020. Understanding pretreatment loss to follow-up of tuberculosis patients: an explanatory qualitative study in Chennai, India. *BMJ global health,* 5**,** e001974.

THOMAS, J. & HARDEN, A. 2008. Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC medical research methodology,* 8**,** 45.

TIEMERSMA, E. W., VAN DER WERF, M. J., BORGDORFF, M. W., WILLIAMS, B. G. & NAGELKERKE, N. J. 2011. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PloS one,* 6**,** e17601.

TIMIRE, C., SANDY, C., KUMAR, A. M., NGWENYA, M., MURWIRA, B., TAKARINDA, K. C. & HARRIES, A. D. 2019. Access to second-line drug susceptibility testing results among patients with Rifampicin resistant tuberculosis after introduction of the Hain® Line Probe Assay in Southern provinces, Zimbabwe. *International Journal of Infectious Diseases,* 81**,** 236-243.

TOMÁS, B. A., PELL, C., CAVANILLAS, A. B., SOLVAS, J. G., POOL, R. & ROURA, M. 2013. Tuberculosis in migrant populations. A systematic review of the qualitative literature. *PLOS one,* 8.

TONG, A., SAINSBURY, P. & CRAIG, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International journal for quality in health care,* 19**,** 349-357.

TOPE, A. T., THOMAS BENJAMIN, T., AGU GEORGIA, C. & ABIODUN ABIGAIL, T. 2014. Can Nigeria sustain the fight against drug resistant mycobacterium tuberculosis. *Journal of Microbiology Research,* 4**,** 72-7.

TROMP, N. & BALTUSSEN, R. 2012. Mapping of multiple criteria for priority setting of health interventions: an aid for decision makers. *BMC health services research,* 12**,** 454.

TUDOR, C., VAN DER WALT, M., MARGOT, B., DORMAN, S. E., PAN, W. K., YENOKYAN, G. & FARLEY, J. E. 2014. Tuberculosis among health care workers in KwaZulu-Natal, South Africa: a retrospective cohort analysis. *Bmc Public Health,* 14.

TURETT, G. S., TELZAK, E. E., TORIAN, L. V., BLUM, S., ALLAND, D., WEISFUSE, I. & FAZAL, B. A. 1995. Improved outcomes for patients with multidrug-resistant tuberculosis. *Clinical Infectious Diseases,* 21**,** 1238-1244.

TWEYA, H., GARETA, D., CHAGWERA, F., BEN-SMITH, A., MWENYEMASI, J., CHIPUTULA, F., BOXSHALL, M., WEIGEL, R., JAHN, A. & HOSSEINIPOUR, M. 2010. Early active follow-up of patients on antiretroviral therapy (ART) who are lost to follow-up: the ‘Back-to-Care’project in Lilongwe, Malawi. *Tropical Medicine & International Health,* 15**,** 82-89.

UKWAJA, K. N., ALOBU, I., ABIMBOLA, S. & HOPEWELL, P. C. 2013a. Household catastrophic payments for tuberculosis care in Nigeria: incidence, determinants, and policy implications for universal health coverage. *Infectious diseases of poverty,* 2**,** 21.

UKWAJA, K. N., ALOBU, I., IGWENYI, C. & HOPEWELL, P. C. 2013b. The High Cost of Free Tuberculosis Services: Patient and Household Costs Associated with Tuberculosis Care in Ebonyi State, Nigeria. *Plos One,* 8.

UKWAJA, K. N., ALOBU, I., MUSTAPHA, G., ONAZI, O. & OSHI, D. C. 2017. 'Sustaining the DOTS': stakeholders' experience of a social protection intervention for TB in Nigeria. *International Health,* 9**,** 112-117.

UKWAJA, K. N., ALOBU, I., NWEKE, C. O. & ONYENWE, E. C. 2013c. Healthcare-seeking behavior, treatment delays and its determinants among pulmonary tuberculosis patients in rural Nigeria: a cross-sectional study. *BMC health services research,* 13**,** 1.

UKWAJA, K. N., ALOBU, I., NWEKE, C. O. & ONYENWE, E. C. 2013d. Healthcare-seeking behavior, treatment delays and its determinants among pulmonary tuberculosis patients in rural Nigeria: a cross-sectional study. *BMC health services research,* 13**,** 25.

UN 2018a. UN General Assembly High-Level Meeting on the fight against tuberculosis. New York: United Nations.

UN 2018b. UN General Assembly, Seventy-third session. *18th plenary meeting.* New York: United Nations.

UPLEKAR, M., WEIL, D., LONNROTH, K., JARAMILLO, E., LIENHARDT, C., DIAS, H. M., FALZON, D., FLOYD, K., GARGIONI, G. & GETAHUN, H. 2015. WHO's new end TB strategy. *The Lancet,* 385**,** 1799-1801.

USAID DHS PROGRAM 1990. Nigeria Demographic and Health Survey 1990.

USAID DHS PROGRAM 1999. Nigeria Demographic and Health Survey 1999.

USAID DHS PROGRAM 2013. Nigeria Demographic and Health Survey 2013.

USAID DHS PROGRAM 2018. Nigeria Demographic and Health Survey 2018.

USHIE, B. A. & JEGEDE, A. S. 2012. The paradox of family support: concerns of tuberculosis-infected HIV patients about involving family and friends in their treatment. *AIDS patient care and STDs,* 26**,** 674-680.

VAN DE WATER, B. J., PRVU BETTGER, J., SILVA, S., HUMPHREYS, J., CUNNINGHAM, C. K. & FARLEY, J. E. 2017. Time to drug-resistant Tuberculosis treatment in a prospective South African Cohort. *Global pediatric health,* 4**,** 2333794X17744140.

VAN DEN HANDEL, T., HAMPTON, K., SANNE, I., STEVENS, W., CROUS, R. & VAN RIE, A. 2015. The impact of Xpert® MTB/RIF in sparsely populated rural settings. *The International Journal of Tuberculosis and Lung Disease,* 19**,** 392-398.

VAN DER WESTHUIZEN, H. & DRAMOWSKI, A. 2017. When students become patients: TB disease among medical undergraduates in Cape Town, South Africa. *South African Medical Journal,* 107**,** 475-479.

VAN HOORN, R., JARAMILLO, E., COLLINS, D., GEBHARD, A. & VAN DEN HOF, S. 2016. The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes - A Systematic Review and Meta-Analysis. *Plos One,* 11**,** 27.

WALSH, D. & DOWNE, S. 2005. Meta-synthesis method for qualitative research: a literature review. *Journal of advanced nursing,* 50**,** 204-211.

WEIBLE, C. M., NOHRSTEDT, D., CAIRNEY, P., CARTER, D. P., CROW, D. A., DURNOVÁ, A. P., HEIKKILA, T., INGOLD, K., MCCONNELL, A. & STONE, D. 2020. COVID-19 and the policy sciences: initial reactions and perspectives. *Policy sciences*, 1-17.

WEIGEL, R., HOCHGESANG, M., BRINKHOF, M. W., HOSSEINIPOUR, M. C., BOXSHALL, M., MHANGO, E., NKWAZI, B., TWEYA, H., KAMLAKA, M. & CHAGWERA, F. 2011. Outcomes and associated risk factors of patients traced after being lost to follow-up from antiretroviral treatment in Lilongwe, Malawi. *BMC infectious diseases,* 11**,** 31.

WHITTEMORE, R. & KNAFL, K. 2005. The integrative review: updated methodology. *Journal of advanced nursing,* 52**,** 546-553.

WHO 2006. WORLD HEALTH STATISTICS 2006,.

WHO 2007. Everybody's business--strengthening health systems to improve health outcomes: WHO's framework for action.

WHO 2010a. The global plan to stop TB 2011-2015: transforming the fight towards elimination of tuberculosis.

WHO 2010b. *Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies*, World Health Organization.

WHO 2013. Definitions and reporting framework for tuberculosis–2013 revision.

WHO 2014a. *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*, World Health Organization.

WHO 2014b. *Global tuberculosis report 2014*, World Health Organization.

WHO 2014c. Health in all policies: Helsinki statement. Framework for country action.

WHO 2015a. Digital health for the End TB Strategy: an agenda for action. World Health Organization.

WHO 2015b. Gear up to end TB: introducing the end TB strategy. World Health Organization.

WHO 2015c. Global reference list of 100 core health indicators. World Health Organization.

WHO 2015d. *Global tuberculosis report 2015*, World Health Organization.

WHO 2015e. Global tuberculosis report 2015.

WHO 2016a. Global tuberculosis report 2016.

WHO 2016b. *WHO treatment guidelines for drug-resistant tuberculosis*, World Health Organization.

WHO 2017a. Global Health Expenditure Database (GHED): total health expenditure. Geneva.

WHO 2017b. *Global tuberculosis report 2017*, World Health Organization.

WHO 2017c. Guidelines for treatment of drug-susceptible tuberculosis and patient care.

WHO 2018a. Engaging private health care providers in TB care and prevention: A landscape analysis. *Geneva: World Health Organization*.

WHO 2018b. *Global tuberculosis report 2018*, World Health Organization.

WHO 2018c. WHO treatment guidelines for multidrug-and rifampicin-resistant tuberculosis, 2018 update. *World Health Organization, Geneva*.

WHO 2019a. Global tuberculosis report 2019.

WHO 2019b. No Time to Wait: Securing the future from drug-resistant infections
- Report to the Secretary-General of the United Nations.

WHO 2019c. No Time to Wait: Securing the future from drug-resistant infections- Report to the Secretary-General of the United Nations.

WHO 2019d. Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. *World Health Organization: Geneva, Switzerland*.

WHO 2019e. *WHO consolidated guidelines on drug-resistant tuberculosis treatment*, World Health Organization.

WHO. 2020a. *Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report, 27 August 2020* [Online]. Available: https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2020.1#.X0ziEX3lNXw.twitter [Accessed].

WHO. 2020b. *Tuberculosis: Key facts* [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/tuberculosis [Accessed].

WHO 2020c. WHO operational handbook on tuberculosis. Module 1: Prevention-Tuberculosis preventive treatment.

WILLIAMS, T. L., & SHAW, R. L. 2016. Synthesizing qualitative research. *In:* (EDS.)., S. (ed.) *International handbook of qualitative methods in sport and exercise.* London: Routledge.

WINGFIELD, T., TOVAR, M. A., HUFF, D., BOCCIA, D., SAUNDERS, M. J., DATTA, S., MONTOYA, R., RAMOS, E., LEWIS, J. J. & GILMAN, R. H. 2016. Beyond pills and tests: addressing the social determinants of tuberculosis. *Clinical medicine,* 16**,** s79.

WORLD HEALTH ORGANIZATION 2010. *Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies*, World Health Organization.

WORLD HEALTH ORGANIZATION 2014. Health in all policies: Helsinki statement. Framework for country action.

WORLD HEALTH ORGANIZATION 2019. Global tuberculosis report 2019.

WORLD HEALTH ORGANIZATION 2020. WHO Tuberculosis Factsheet *World Health Organization Newsroom, Geneva.*

WORLD HEALTH ORGANIZATION STOP TB 2011. Partnership. An international roadmap for tuberculosis research. *Geneva, Switzerland: WHO*.

WORLDOMETERS. 2020. *COVID-19 Coronavirus Pandemic* [Online]. Available: https://www.worldometers.info/coronavirus/ [Accessed 31 March 2020 2020].

WU, S., ROYCHOWDHURY, I. & KHAN, M. 2017. Evaluating the impact of healthcare provider training to improve tuberculosis management: a systematic review of methods and outcome indicators used. *International Journal of Infectious Diseases,* 56**,** 105-110.

YADAV, S. K., DAMOR, R., KANTHARIA, S. & TIWARI, M. 2015. Assessment of Knowledge and Treatment Seeking Behaviour among Tuberculosis and Multi-Drug Resistant Tuberculosis Patients:-A Case Control Study. *IOSR Journal of Dental and Medical Sciences,* 14**,** 66-71.

YAMEY, G. & GONSALVES, G. 2020. Donald Trump: a political determinant of covid-19. British Medical Journal Publishing Group.

YANG, W.-T., GOUNDER, C. R., AKANDE, T., DE NEVE, J.-W., MCINTIRE, K. N., CHANDRASEKHAR, A., DE LIMA PEREIRA, A., GUMMADI, N., SAMANTA, S. & GUPTA, A. 2014. Barriers and delays in tuberculosis diagnosis and treatment services: does gender matter? *Tuberculosis research and treatment,* 2014.

YASSIN, M. A., DATIKO, D. G., TULLOCH, O., MARKOS, P., ASCHALEW, M., SHARGIE, E. B., DANGISSO, M. H., KOMATSU, R., SAHU, S. & BLOK, L. 2013a. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. *PloS one,* 8**,** e63174.

YASSIN, M. A., DATIKO, D. G., TULLOCH, O., MARKOS, P., ASCHALEW, M., SHARGIE, E. B., DANGISSO, M. H., KOMATSU, R., SAHU, S. & BLOK, L. 2013b. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. *PloS one,* 8.

YIN, R. K. 2013. Case Study Research Design and Methods, 5th Revised. Sage Publications Inc.

ZAROWSKY, C., HADDAD, S. & NGUYEN, V.-K. 2013. Beyond 'vulnerable groups': contexts and dynamics of vulnerability. *Global Health Promotion,* 20**,** 3-9.

ZIMBABWE NATIONAL TB CONTROL PROGRAMME 2010. National Tuberculosis Guidelines. *In:* HEALTH, N. D. O. (ed.). Republic of South Africa: Zimbabwe National TB Control Programme,.

ZIMRI, K., HESSELING, A. C., GODFREY-FAUSSETT, P., SCHAAF, H. S. & SEDDON, J. A. 2012. Why do child contacts of multidrug-resistant tuberculosis not come to the assessment clinic? *Public Health Action,* 2**,** 71-75.

APPENDICES

Appendix 1: Study Instruments

1A Key Informant Recruitment Letter

Dear [name of potential key informant]

My name is Charity Omenka. I am a doctoral student at the University of Montreal, Quebec, Canada.

This is to follow up on our discussion on [date of initial contact] regarding a study titled "*Patient socio-demographic characteristics and timely treatment initiation of free DRTB treatment in Nigeria- a mixed methods study*".

I am now beginning the formal data collection to investigate further the issues around patient treatment initiation on the free DRTB services and would like to ask your permission for an interview as part of my research. As a [name key informant's designation] from the [name of key informants' institution], your insight into the study is very valuable. The interview would involve an approximate one hour in-person discussion with you on questions pertaining to your experience and involvement in Nigeria's DRTB services and related health issues. With your permission, the interview will be audio-recorded. You will have the opportunity to review the transcription for verification.

I will be in Nigeria for data collection in May 2017. I will contact you upon my arrival to give you more information and agree on a time for meeting, if you agree to participate. If you are interested in participating, please contact me. Also, if you have any questions prior to our meeting, please contact me.

Thank you for your time.
Charity Oga Omenka

1B: Participant Information Sheet and Informed Consent Form

Participant Information and Informed Consent Form

Title of the study: ***Patient socio-demographic characteristics and timely treatment initiation for free DRTB treatment in Nigeria- a mixed methods study***

Principal investigator
Charity Oga Omenka, University of Montreal, Quebec, Canada

Academic supervisors
Prof. Christina Zarowsky, University of Montreal, Quebec, Canada

Prof. Richard Menzies, McGill University, Quebec, Canada

Introduction
We invite you to take part in a research study being conducted by Charity Omenka, a doctoral student at the University of Montreal, as part of her Doctor of Public Health degree. Your participation in this study is voluntary and you may withdraw from the study at any time. The study is described below. This description tells you about the risks, inconvenience, or discomfort which you might experience. Please feel free to discuss any words or information that you do not clearly understand or questions you may have about this study with Charity Omenka.

Purpose of the study
The purpose of this study is to learn about any relationships between patient gender, income, age, place of residence and treatment initiation for drug-resistant tuberculosis (DRTB) and to explore the dynamics of access to care from the perspectives of healthcare providers, patients and their families.

What will happen
The study will include group discussions with DR TB patients, and one-on-one interview with Charity Omenka, each of which will last approximately 1 and half hour. Questions about your experiences with the DR TB health service delivery, either as a provider or as a patient, will be the focus of all discussions or interviews. With your permission, interviews will be audio-recorded and transcribed. You will have the opportunity to verify the transcript of the interview. The transcripts of these interviews as well as notes will be analyzed by Charity Omenka to find common themes and important differences among the responses. The results will be presented in several different ways. They will be included in academic papers and conferences. A formal report will also be returned to Nigeria's DRTB program. Interviews will be conducted at a time and place that is convenient for you. The transcript of the interview will be delivered to you for review and verification.

Possible risk and discomforts

There is very little risk in participating in this study. The interview may touch on any issues you may have experienced with access to DRTB treatment. If there is anything that you would prefer not to discuss, please feel free to say so. No offense will be taken, and there will be no negative consequences if you would prefer not to answer a question. We would appreciate your guidance should if you see any question as intrusive. In the event that you experience any stress or discomfort from your involvement in this study, we ask that you contact *the designated counselor* at (+234 --------) to discuss the situation.

Possible benefits

There are no direct benefits of participation. Although not guaranteed, possible indirect benefits include using information collected to inform future DRTB program decisions in areas of patient access and needs of different socio-demographic groups.

Confidentiality

Personal records collected during this research will be kept locked away at all times. No names will be used with the final research reports and we ask that you do not to disclose anything you hear or who participated in this study to protect the confidentiality of other participants. We will refer to you or your words using a pseudonym or invented name, which we invite you to choose and fill below. You also have the option to review and approve any direct quotes in text that are chosen for inclusion in final results before they are published.

Every member of the data collection team will be required to sign a confidentiality agreement. During the focus groups we ask that all participants respect and maintain the confidentially of the discussion; however, it is not possible for the researchers to guarantee that everyone will do so.

Audiotapes of the group discussion will be typed and used to prepare a report. The audiotapes and typed notes will be kept for 5 years in a secure locked file cabinet and office. Only the research will have access to them and know your name

Questions

If you have any questions about this study, please contact Charity Omenka in person when she is with you at any other time.

Problems or concerns

If you have any difficulties with, or wish to voice concern about, any aspect of your participation in this study, you may contact Prof Christina Zarowsky, of the Université de Montréal and the Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM).

INFORMED CONSENT SIGNATURE

Title of the study: ***Patient socio-demographic characteristics and timely treatment initiation for free DRTB treatment in Nigeria- a mixed methods study***

Principal investigator
Charity Oga Omenka, University of Montreal, Quebec, Canada

Academic supervisors
Prof. Christina Zarowsky, University of Montreal, Quebec, Canada

Prof. Richard Menzies, McGill University, Quebec, Canada

To be completed by the research participant: Circle Yes or No

1. Do you feel you have received sufficient information to participate in this research? Yes No
2. Do you understand that you are about to participate in a research project? Yes No
3. Have you had an opportunity to ask questions and discuss this study with a member of the research team? Yes No
4. Do you understand the benefits and risks in participating in this study? Yes No
5. You are free to refuse to participate or withdraw from this study at any time. You will not have to offer a reason and this will not affect you. All the interview information provided will be discarded at this time. Is this understood? Yes No
6. Have the issues of confidentiality and anonymity been explained? Yes No
7. Do you give permission for the use of full quotations in the written results? Your name will not be used. You will be given the opportunity to see the quote in text and make a final decision on whether it is used or not. Yes No
8. Would you like to review and confirm the accuracy of your interview transcripts? Yes No
9. Would you like to receive a copy of the final report? Yes No
10. Do you give permission to have the interview audio-recorded? Yes No

Please indicate that you have given your consent by signing below:
Signature of Research Participant: ______________________________
Printed Name: ____
Signature of Witness: ____
Printed Name: ____
Date: ____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.
Signature of Researcher or Designee: __________________________ Date: ____________________

THE INFORMATION SHEET IS ATTACHED TO THIS CONSENT FORM

1C: Key Informant Participant Semi-Structured Interview Guide (for Policy-makers, and health workers)

Preamble

Today, I'm going to be asking you some questions about the institution you work for and the roles and responsibilities of your position in relation to DRTB diagnosis and treatment. As [insert key informants role] your insights are valuable to this topic. Please note that there is no right or wrong answer to any of the questions. Do you have any questions before we begin?

Ok, shall we begin? [As you have given permission to audio-record, I am going to turn the recorder on now…]

Roles & Responsibilities of Key Informant

1. What is your job title what organization do you work with?
2. What are your main duties, especially with regards to DRTB services?
3. Can you tell me about a typical day or week at work?

Follow-up and probing questions:

Can you explain to me how the process works? [to clarify any reference to structures, processes or policies]

Policies, Structures and Processes

1. What does the DRTB program guideline say about timeliness for DRTB diagnosis and treatment?
2. What are the structures in place (funding, stakeholders, coverage, facilities, equipments, health supplies, interventions, providers etc) to ensure this happens? Nationally? In Ogun State?
3. How is it being operationalized? What are the current processes for patient diagnosis and treatment?
4. What are the major strengths of this program?
5. What are the major complaints about the program that you have heard from providers or patients?
6. What part of the structures, processes or program guidelines do you think can be improved upon? In what way?

Specific for National Program Managers

7. What is the total number of DRTB service points (or by program area) in Nigeria, broken by States?
8. What is the percentage coverage of those in need and source of data?
9. What is the Government and partners doing to improve access to DRTB services?
10. Please can you direct me to where I can get and review relevant documentation on existing programmes in the Nigeria?
11. What has been some of the challenges to improving access to DRTB in the Nigeria?

Equity and treatment access by socio-demographic groups

1. Do you think these affect men or women differently? Or married or unmarried individuals? Or children differently from adults? Or people who live in rural areas versus those in urban areas?
2. What group of patients are likely to have the most difficulty accessing diagnosis or treatment?
3. Is there any indication that women or children or rural-dwellers or married individuals might encounter barriers in receiving care compared with men, adults, urban-dwellers or unmarried individuals?
4. Do the differences in life, social, economic, and familial experiences of men and women affect their ability to receive care in this program?
5. What resources might an individual need to benefit from this program? Do all groups of patients have equal access to these necessary resources?

Follow-up and probing questions: (Reasons for these differences)
Follow-up questions are for exploring specific issues that are raised during the discussion in more detail. Specifically ask for more details or possible reasons for the differences mentioned above, if any.

Pathway to care

1. How long do you think it takes a patient to receive a diagnosis once s/he comes to the hospital?
2. How long do you think patients wait to be placed on treatment after diagnosis?
3. Where else might a patient go before coming to the DRTB clinic for diagnosis? What other alternatives to the DRTB program do you think patients try before coming to the clinic?
4. Do you think patients are being lost to care? Why reasons can you think of for this happening?

Closing

1. Do you have any question for me?
2. From the consent form, I see that you indicated you (do not want) wanted to review the transcribed copies. I will have it sent to you by ___________________ and you can please let me know if I got anything wrong. I will be here for a couple more days if you have anything additional you want to say.
3. Thank you very much for your time

1D: Key Informant Participant Semi-Structured Interview Guide (for patient relatives, and patients who are not on treatment)

Preamble

Today, I'm going to be asking you some questions about your (or your family member's) experience with DR TB diagnosis and treatment. We are trying to find out what prevents patients from getting DRTB services. It's not always easy for patients coming to the clinic for care. Please feel free to be open about challenges you face with these. Everything you say here will remain confidential, and your personal information will not be shared with anyone at the clinic. Do you have any questions before we begin?

Ok, shall we begin? [As you have given permission to audio-record, I am going to turn the recorder on now…]

Socio-demographic information

a) Sex (M / F) b) Age (Years) c) Marital status
d) Educational level e) Occupation e) Distance from facility (in time or distance) f) Cost of care in terms of transport & services

Policies, Structures and Processes

1. What do you know about DRTB? (Allow patient to say whatever, and then probe on the following: cause of infection, prevention, treatment availability, outcomes).
2. Apart from these, is there anything else you have heard from your community that explains DRTB in a different way?
3. What are the current processes for a patient to be diagnosed or treated?
4. What has been your (and) greatest challenge with regards to DRTB care?
5. List all the problems you face accessing care in order of importance to you.
6. What are the major strengths of this program? Weaknesses? How can these be improved?

Equity and treatment access by socio-demographic groups

1. Have you (or your family member) ever had any experience of being treated differently because of age, sex, marital status or place or residence?
2. Do you think anyone is treated differently or is having more difficulty accessing these services? What kind of person would this be? (probe child, marital status, place of residence, sex)
3. Have you heard that women or children or rural-dwellers or unmarried individuals might encounter barriers in receiving care compared with men, adults, urban-dwellers or married individuals?
4. What resources does one need to benefit from this program? Do you (or your family member) have equal access to these necessary resources? Why or why not?
5. How much have you (or your family member) had to pay to access these services? Transport? Food? Drugs? Registration? Lab tests?

6. What have (would) you and/or your family had (have) to give up in order to be able to receive care? (probe employment, informal income)

Follow-up and probing questions: (Reasons for these differences)
Follow-up questions are for exploring specific issues that are raised during the discussion in more detail. Specifically ask for more details or possible reasons for the differences mentioned above, if any.

Pathway to care

1. How long does (did) it take (your family member) to receive a diagnosis (in days)?
2. How long to be placed on treatment after diagnosis (in days)?
3. Where else have you (or your loved one) received any care for DRTB? (probe pharmacy, traditional healer, other)
4. Have you (or family member) ever missed an appointment at the hospital? (Reasons, and details on type of consultation)
5. In your dealings with the DRTB clinic, were you given the chance to state your problems and ask questions? Yes No
6. Were you treated with respect? Yes No
7. Do you feel you can trust the health workers? Yes No
8. If there is another centre offering services closer to your house, would you go there? Reasons for answer

Closing

1. Do you have any question for me?
2. From the consent form, I see that you indicated you (do not want) wanted to review the transcribed copies. I will have it sent to you by ___________________ and you can please let me know if I got anything wrong. I will be here for a couple more days if you have anything additional you want to say.
3. Thank you very much for your time

1E: FOCUS GROUP DISCUSSION (with patients on treatment)

Focus Group Discussions
Preamble

1. Welcome: Introduction of research team present.
2. Overview of research: Today, I'm going to be asking you some questions about your (or your family member's) experience with DR TB diagnosis and treatment. We are trying to find out what prevents patients from getting DRTB services. It's not always easy for patients coming to the clinic for care. Please feel free to be open about challenges you face with these. Everything you say here will remain confidential, and your personal information will not be shared with anyone at the clinic. Do you have any questions before we begin?
3. Informed consent process

[Answer any questions and confirm that everyone is consenting to audio-recording the discussions]

Socio-demographic information

a) Sex (M / F) b) Age (Years) c) Marital status
d) Educational level e) Occupation e) Distance from facility (in time or distance) f) Cost of care in terms of transport & services

Policies, Structures and Processes

1. What are the general beliefs about DRTB (guide discussion if necessary with the following points: cause of infection, prevention, treatment availability, outcomes)?
2. What has been your experience so far with regards to receiving DRTB services?
3. How would you describe the current processes for a patient to be diagnosed or treated?
4. What do you think are the strengths of this program? The weaknesses? Can you think of any way the program can be improved?

Equity and treatment access by socio-demographic groups

1. Has anyone you know ever had any experience of being treated differently here because of age, sex, marital status or place or residence?
2. Do you think anyone is treated differently or is having more difficulty accessing these services? What kind of person would this be? (probe child, marital status, place of residence, sex)
3. How much do people pay to access these services? Transport? Food? Drugs? Registration? Lab tests?
4. What have patients like you had to give up in order to be able to receive care? (probe employment, informal income)
5. Are there some factors that prevent people from accessing DRTB services here?
6. How do you think these barriers can be handled: by the facilities, the government, the community and by the individuals?

Pathway to care

1. How long does it take to receive a diagnosis (in days)? (probe for specific examples, shortest and longest periods etc)
2. How long did it take for the doctor to place you on treatment after diagnosis (in days)?
3. Where else have you received any care for DRTB? (probe pharmacy, traditional healer, other)
4. Have you ever missed an appointment at the hospital? (Reasons, and details on type of consultation)
5. If there is another centre offering services closer to your house, would you go there? Reasons for answer

Closing

4. Do you have any question for me?
5. I would like to discuss the transcripts of this interview with anyone of you who can be available so you can please let me know if I got anything wrong. I will contact anyone who has indicated in his/her consent form to correct the transcript.
6. Thank you very much for your time

Appendix 2: Sample Coding Tree Using Quirkos Software

INDUCTIVE

DEDUCTIVE


Gap 1– never tested for drtb…
(no description)
Misdiagnosis | 11
(no description)
lack of HCW knowledge | 1
(no description)
patient awareness | 3
(no description)
Alternative care (after mis…
(no description)
postponed appointments …
(no description)
Private HCW attitude | 3
(no description)
Coverage | 4 (5)
(no description)
Geogr location | 1
(no description)
Religious belief | 1
(no description)
self medication | 1
(no description)
Gap 2: Never diagnosed | 0 …
(no description)
delayed diagnosis | 8 (9)
(no description)
cultural norms | 1
(no description)
Costs | 2
(no description)
stigma | 5
(no description)
deadly | 1
(no description)
alternate care | 1
(no description)
Gap 3 – Never placed on tre…
(no description)
diagnosed too late | 2
(no description)
Gap 4– Never completed tre…
(no description)
Public HCW attitude | 3
(no description)
side effectss | 6
(no description)
treatment duration | 4
(no description)
treatment duration | 1
(no description)
difference Comm/hosp | 2
(no description)
health talks | 1
(no description)
Health center privileges | 1
(no description)

Appendix 3: Ethics Certificates

6A : CRCHUM initial and renewal certificates

CHUM

Comité d'éthique de la recherche du CHUM
Pavillon R, 900 rue St-Denis, 3e étage
Montréal (Québec) H2X 0A9

Le 06 juin 2017

Madame Christina Zarowsky
Axe de recherche : santé mondiale

a/s: Mme Charity Oga Omenka

Objet :	**17.060 – Approbation initiale et FINALE CÉS**
	Influences intersectorielles des caractéristiques socio-démographiques des patients, sur l'initiation précoce du traitement de la tuberculose multi-résistante dans les services de santé au Nigéria. Une étude mixte.

Madame,

Le Comité d'évaluation scientifique du CHUM, à sa réunion plénière tenue à Montréal le 06 juin 2017, a évalué le projet mentionné en rubrique.

Après évaluation et discussion, le projet est approuvé tel quel à l'unanimité et sera transmis au CÉR du CHUM pour évaluation et approbation lors d'une prochaine réunion.

Il est entendu que vous ne pouvez commencer le recrutement de sujets avant d'avoir obtenu l'approbation finale du comité d'éthique de la recherche.
Veuillez noter que le projet de recherche ne pourra débuter avant que vous n'ayez reçu la lettre d'autorisation de réaliser la recherche dans les murs de l'établissement.

Pour toute question relative à cette correspondance, veuillez communiquer avec la personne soussignée via NAGANO, ou avec le secrétariat du comité, par courriel ou téléphone : ethique.recherche.chum@ssss.gouv.qc.ca – **514 890-8000 poste 14485.**

Vous souhaitant la meilleure des chances dans la poursuite de vos travaux, nous vous prions d'accepter, nos salutations distinguées.

Dr Benoit Coutu, MD
Président du CÉS du CHUM

CHUM

Comité d'éthique de la recherche du CHUM
Pavillon R, 900 rue St-Denis, 3e étage
Montréal (Québec) H2X 0A9

Formulaire de demande de renouvellement annuel de l'approbation d'un projet de recherche

Date de dépôt du formulaire : **2019-07-09 17:08**
Date d'approbation du projet par le CER : **2017-06-12**
Numéro(s) de projet : **2018-7257, 17.060 - MJB**
Statut du formulaire : **Approuvé**

Déposé par : **Omenka, Charity Oga**
Identifiant Nagano : **IPASTTI**
Formulaire : **F9 - 38693**

Suivi du BCER

1. **Statut de la demande:**
   Demande approuvée

2. **La demande a été traitée par :**
   Lynda Ferlatte
   date de traitement:
   2019-07-13

3. **Renouvellement accordé**
   Projet en retard de renouvellement. EXCEPTIONNELLEMENT, nous avons procédé au renouvellement du projet pour deux ans, soit du 12 juin 2018 au 12 juin 2020, afin de régulariser la situation.

Section 1 - Renseignements généraux

1. **Indiquez, en français, le titre complet du projet de recherche**

   Influences intersectorielles des caractéristiques socio-démographiques des patients, sur l'initiation précoce du traitement de la tuberculose multi-résistante dans les services de santé au Nigéria. Une étude mixte.

6B : Nigeria National Health Research Ethics Committee Certificate

National Health Research Ethics Committee of Nigeria (NHREC)

Promoting Highest Ethical and Scientific Standards for Health Research in Nigeria

Federal Ministry of Health

NHREC Protocol Number NHREC/01/01/2007-06/04/2017
NHREC Approval Number NHREC/01/01/2007-15/05/2017
Date: 15 May, 2017

Re: Intersecting Influences of Patient socio-demographic Characteristics on Timely Treatment Initiation of free DRTB Services in Nigeria a mixed Methods Study.

Health Research Committee assigned number: NHREC/01/01/2007
Name of Student Investigator: Charity Oga Omenka
Address of Student Investigator: [redacted]

Date of receipt of valid application: 06/04/2017
Date when final determination of research was made: 15/05/2017

Notice of Expedited Committee Review and Approval

This is to inform you that the research described in the submitted protocol, the consent forms, advertisements and other participant information materials have been reviewed and *given expedited committee approval by the National Health Research Ethics Committee.*

This approval dates from 15/05/2017 to 14/05/2018. If there is delay in starting the research, please inform the HREC so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study.* In multiyear research, endeavour to submit your annual report to the HREC early in order to obtain renewal of your approval and avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserves the right to conduct compliance visit your research site without previous notification.

Signed

[redacted]

Professor Zubairu Iliyasu MBBS (UniMaid), MPH (Glasg.), PhD (Shef.), FWACP, FMCPH
Chairman, National Health Research Ethics Committee of Nigeria (NHREC)

Department of Health Planning, Research & Statistics
Federal Ministry of Health
11th Floor, Federal Secretariat Complex Phase III
Ahmadu Bello Way, Abuja

Tel: +234-09-523-8367
E-mail: chairman@nhrec.net, secretary@nhrec.net, deskofficer@nhrec.net,
URL: http://www.nhrec.net,

6C : University of Montreal CERES Certificate

Université de Montréal

CERSES-19-098-D

Comité d'éthique de la recherche en sciences et en santé (CERSES)

CERTIFICAT D'APPROBATION ÉTHIQUE

Le Comité d'éthique de la recherche en sciences et en santé (CERSES), selon les procédures en vigueur, en vertu des documents qui lui ont été fournis, a examiné le projet de recherche suivant et conclu qu'il respecte les règles d'éthique énoncées dans la Politique sur la recherche avec des êtres humains *de l'Université de Montréal.*

Projet	
Titre du projet	**Influences intersectorielles des caractéristiques socio-démographiques des patients, sur l'initiation précoce du traitement de la tuberculose multi-résistante dans les services de santé au Nigéria. Une étude mixte.**
Étudiant requérant	**Charity Oga-Omenka**, Candidate au doctorat, Ecole de santé publique
Sous la direction de:	Christina Zarowsky, Faculté de médecine - Département de médecine sociale et préventive, Université de Montréal & Richard Menzies, Faculté de médecine, Université McGill.

Financement	
Organisme	Institute of Human Virology, Nigeria
Programme	Global Fund New Funding Model MDR TB Grant
Titre de l'octroi si différent	
Numéro d'octroi	
Chercheur principal	
No de compte	

MODALITÉS D'APPLICATION

Tout changement anticipé au protocole de recherche doit être communiqué au Comité qui en évaluera l'impact au chapitre de l'éthique.

Toute interruption prématurée du projet ou tout incident grave doit être immédiatement signalé au Comité.

Selon les règles universitaires en vigueur, un suivi annuel est minimalement exigé pour maintenir la validité de la présente approbation éthique, et ce, jusqu'à la fin du projet. Le questionnaire de suivi est disponible sur la page web du Comité.

[redacted]

Marie-Josée Bernardi, vice-présidente
Comité d'éthique de la recherche en sciences et en santé (CERSES)
Université de Montréal

26 septembre 2019
Date de délivrance

1er octobre 2020
Date de fin de validité

1er octobre 2020
Date du prochain suivi

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

adresse civique
3333, Queen Mary
Local 220-3
Montréal QC H3V 1A2

Téléphone : 514-343-6111 poste 2604
cerses@umontreal.ca
www.cerses.umontreal.ca

Université de Montréal

Comité d'éthique de la recherche en sciences et en santé (CERSES)

26 septembre 2019

Objet: Approbation éthique – « Influences intersectorielles des caractéristiques socio-démographiques des patients, sur l'initiation précoce du traitement de la tuberculose multi-résistante dans les services de santé au Nigéria. Une étude mixte. »

Mme Charity Oga-Omenka,

Le Comité d'éthique de la recherche en sciences et en santé (CERSES) a étudié le projet de recherche susmentionné et a délivré le certificat d'éthique demandé suite à la satisfaction des exigences précédemment émises. Vous trouverez ci-joint une copie numérisée de votre certificat. Nous vous invitons à faire suivre ce document au technicien en gestion de dossiers étudiants (TGDE) de votre département.

Notez qu'il y apparaît une mention relative à un suivi annuel et que le certificat comporte une date de fin de validité. En effet, afin de répondre aux exigences éthiques en vigueur au Canada et à l'Université de Montréal, nous devons exercer un suivi annuel auprès des chercheurs et étudiants-chercheurs.

De manière à rendre ce processus le plus simple possible, nous avons élaboré un court questionnaire qui vous permettra à la fois de satisfaire aux exigences du suivi et de nous faire part de vos commentaires et de vos besoins en matière d'éthique en cours de recherche. Ce questionnaire de suivi devra être rempli annuellement jusqu'à la fin du projet et pourra nous être retourné par courriel. La validité de l'approbation éthique est conditionnelle à ce suivi. Sur réception du dernier rapport de suivi en fin de projet, votre dossier sera clos.

Il est entendu que cela ne modifie en rien l'obligation pour le chercheur, tel qu'indiqué sur le certificat d'éthique, de signaler au CERSES tout incident grave dès qu'il survient ou de lui faire part de tout changement anticipé au protocole de recherche.

Nous vous prions d'agréer, Mesdames, Monsieur, l'expression de nos sentiments les meilleurs,

Marie-Josée Bernardi, vice-présidente
Comité d'éthique de la recherche en sciences et en santé (CERSES)
Université de Montréal

c.c. Gestion des certificats, BRDV
Christina Zarowsky, Faculté de médecine - Département de médecine sociale et préventive
Richard Menzies, Faculté de médecine
p.j. Certificat #CERSES-19-098-D

adresse postale
C.P. 6128, succ. Centre-ville
Montréal QC H3C 3J7

adresse civique
3333, Queen Mary
Local 220-3
Montréal QC H3V 1A2

Téléphone : 514-343-6111 poste 2604
cerses@umontreal.ca
www.cerses.umontreal.ca